MAY 21 1917
UNIV. OF MICH. LIBRARY

VOLUME 19 IN TWO PARTS—PART I NUMBER 5

THE ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston
THEO. C. JANEWAY, Baltimore
GEORGE DOCK, St. Louis
WARFIELD T. LONGCOPE, New York

W. S. THAYER, Baltimore

MAY 15, 1917

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879

CONTENTS OF VOLUME XIX

JANUARY, 1917. NUMBER 1

PAGE

THE CLINICAL VALUE OF AMBARD'S COEFFICIENT OF UREA EXCRETION. D. SLATER LEWIS, M.D., BALTIMORE 1

THE ACTION OF THE SEVERAL "FEMALE REMEDIES" ON STRIPS OF THE EXCISED HUMAN UTERUS. J. D. PILCHER, M.D., OMAHA 53

THE PRESENT SIGNIFICANCE OF THE AMINO-ACIDS IN PHYSIOLOGY AND PATHOLOGY. DONALD D. VAN SLYKE, PH.D., NEW YORK 56

PROGRESSIVE MUSCULAR DYSTROPHY AS AN ENDOCRINE DISEASE. WALTER TIMME, M.D., NEW YORK 79

BLOOD CHANGES IN ALBINO RATS FOLLOWING REMOVAL OF THE SPLEEN. C. C. WOLFERTH, M.D., PHILADELPHIA 105

EXPERIMENTS ON THE ORIGIN AND CONDUCTION OF THE CARDIAC IMPULSE. VII. SINOVENTRICULAR AND SINO-AURICULAR HEART-BLOCK. J. A. E. EYSTER, M.D., AND WALTER J. MEEK, PH.D., MADISON, WIS. 117

THE OCCURRENCE OF NUCLEAR CHANGES IN THE RED BLOOD CELLS FOLLOWING SPLENECTOMY. QUINTER O. GILBERT, M.D., ANN ARBOR, MICH. ... 140

THE EFFECT OF HEAT AND CONTINUOUS INCANDESCENT ELECTRIC LIGHT IN EXPERIMENTAL ARTHRITIS. WALTER E. SIMMONDS, M.D., AND J. J. MOORE, M.S., M.D., CHICAGO 153

FURTHER QUANTITATIVE STUDY OF THE DUODENAL BLOOD-DERIVED PIGMENTS. J. P. SCHNEIDER, M.D., MINNEAPOLIS 156

FEBRUARY, 1917. NUMBER 2

PAGE

OSTEOGENESIS IMPERFECTA. JULIUS H. HESS, M.D., CHICAGO 163

HEREDITARY HEMORRHAGIC TELANGIECTASIA, WITH REPORT OF THREE FAMILIES AND A REVIEW OF THOSE PREVIOUSLY RECORDED. WALTER R. STEELE, M.D., HARTFORD, CONN. 194

A CLINICAL STUDY OF THE SECRETIONS ON THE PROXIMAL AND DISTAL SIDES OF THE PYLORUS. A. S. ROBINSON, M.D., CLEVELAND 220

THE RELATION OF HYPERTROPHIC OSTEO-ARTHROPATHY TO PULMONARY TUBERCULOSIS. LEO KESSEL, M.D., NEW YORK 239

TYPHOIDIN QUOTIENTS. AN ANALYSIS OF THE FACTORS OF UNCERTAINTY IN THE CUTANEOUS TYPHOIDIN TEST. EUGENE S. KILGORE, SAN FRANCISCO 263

A COMPARISON OF TWO METHODS OF VACCINATING AGAINST TYPHOID FEVER. EUGENE S. KILGORE, SAN FRANCISCO 276

THE AGGLUTININS AND COMPLEMENT-FIXING ANTIBODIES IN THE SERUM OF PERSONS VACCINATED AGAINST TYPHOID FEVER. K. F. MEYER AND EUGENE S. KILGORE, SAN FRANCISCO 293

d-GLUCOSE TOLERANCE IN HEALTH AND DISEASE. RUSSELL M. WILDER, M.D., AND W. D. SANSUM, M.D., CHICAGO 311

The Archives of Internal Medicine

Vol. XIX MAY, 1917.—IN TWO PARTS. PART I. No. 5

AN EXPERIMENTAL TEST OF THE RELATION OF SEWAGE DISPOSAL TO THE SPREAD OF PELLAGRA *

J. F. SILER, M.D.
Major, Medical Corps, U. S. Army

P. E. GARRISON, M.D.
Passed Asst. Surg., U. S. Navy

AND

W. J. MacNEAL, M.D.

NEW YORK

INTRODUCTION

In September, 1913, we[1] called attention to the apparent relation between the origin of new cases of pellagra and the employment of insanitary methods of sewage disposal. This relationship has been discussed in several subsequent publications of this commission, and we have offered the hypothesis that the methods of disposal of human wastes might prove to be a determining factor in the spread of pellagra in certain communities. A practical experiment was announced and described in our second progress report.[2] Since that time our epidemiologic observations on this particular point have been supported by other independent observers in Charleston, S. C.,[3] and in Nashville, Tenn.[4]

* Submitted for publication Dec. 12, 1916.

* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* Read in part before the Society for Experimental Biology and Medicine, Nov. 15, 1916.

* The epidemiologic surveys in 1915 and 1916, utilized in this paper, have been made since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy and U. S. Army, respectively. The paper itself has been written since that time. They are, therefore, not personally responsible for the observations of the last two years, for the compilation of the data, or for the deductions drawn from them.

1. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: A Summary of the First Progress Report of the Thompson-McFadden Pellagra Commission. Read at the Special Pellagra Conference at Spartanburg, S. C., Sept. 3, 1913; Jour. Am. Med. Assn., Jan. 3, 1914, **62**, 8.

2. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: The Relation of Methods of Disposal of Sewage to the Spread of Pellagra, THE ARCHIVES INT. MED., 1914, **14**, 453; Second Progress Report, New York, 1915, p. 96.

3. Smith, W. A.: Epidemiology of Pellagra in Charleston, S. C. Read at the Third Triennial Pellagra Conference, Columbia, S. C., October, 1915.

4. Jobling, J. W., and Peterson, W.: A Preliminary Report on the Epidemiology of Pellagra in Nashville, Tenn., Jour. Infect. Dis., 1916, **18**, 501.

THE EXPERIMENT

In the present communication we wish to present the results of the experiment begun in the community of Spartan Mills, Spartanburg, South Carolina, in 1913. This particular community had been a conspicuous endemic center of pellagra as long as the disease had been recognized in this region. Our records show that five new cases of pellagra were known to have appeared in this mill village previous to 1909, five in 1909, thirteen in 1910, twenty-three in 1911, eight in 1912 and thirty in 1913. In the fall of 1913 the installation of a water-carriage system of sewerage was begun, and the actual house connections were made as rapidly as the progress of the work would permit. One house was equipped in August, 1913; five houses in September, 1913; five blocks of houses in December, 1913; three blocks in January, 1914; three blocks in March; five blocks in April and seven blocks in May, 1914. A small group of houses, six in number, situated on very uneven ground at one corner of the mill property, was left without sewer connection. These houses were equipped with fly-proof pail closets. All the old, open, unscreened surface privies were demolished and removed. We had made a complete house-to-house survey of this community and of some of the adjoining groups of houses in 1913, and had accumulated rather extensive but, of course, much less complete records of the pellagrins there in previous years. The house-to-house survey was again made in 1914, in 1915 and in 1916, and in these years the survey was also extended to some of the neighboring districts.

In 1914 considerable attention was given by the Spartanburg Health Department to the privies everywhere in the city, and the owners of the houses adjacent to Spartan Mill, which is within the city limits, were compelled to make all privies fly-tight and leak-proof in that year. Subsequently, many of these privies have been maintained in a fairly sanitary condition, but others have fallen into a state of dilapidation, such that they are, from the point of view of disease dissemination, not at all different from the old surface privies. On the other hand, the sewered closets of the mill houses, which were occasionally stopped up or out of use because of ignorance of the population during the first year, have become more and more efficient as the people have become accustomed to their use and have recognized the ease with which they can be kept clean. It should also be mentioned that the houses on the mill property all belong to the mill company and are rented to their employees, who, as a rule, are not property owners. The houses on the neighboring property are privately owned and frequently occupied by the owners, and, if rented, are generally rented to people in better financial circumstances than the mill population.

THE RESULTS

From 1908 to and including 1913, eight[5] new cases of pellagra appeared in the houses immediately adjacent to the mill property, which have been included in this survey. During the same time there arose eighty-three[6] new cases within the mill property. Table 1 shows the number of new pellagrins that appeared in each of these two sections in each year since 1908. The population living on the mill property was approximately 2,000 people, and that in the adjacent houses included in this survey approximately 300.

TABLE 1.—PELLAGRINS INCIDENT IN SPARTAN MILLS AND IN THE ADJACENT SURVEYED DISTRICT IN EACH YEAR

	1908	1909	1910	1911	1912	1913	1914	1915	1916
In Spartan Mills.....	4	5	13	23	8	30	18	8	2
In adjacent district.....	0	2	0	1	3	2	3	2	4

During the year 1914, in which the sewer connections were completed, eighteen persons developed initial symptoms on the mill property. One arose in a house which was sewered in December, 1913, but just across the street from a house in which pellagrins were living, and which was not connected to the sewer until May, 1914. One arose in a house well within the district sewered in December, 1913. This patient was a married woman, whose mother, Pellagrin 237, had suffered from pellagra for many years. The mother lived in the neighboring unsewered district and was frequently visited by her daughter. Three cases appeared in a section which was sewered in January, 1914, eight arose in a section which was connected with the sewer in March, 1914, one in a section connected with sewer in April, and the remaining four in a section which was connected with the sewer in May, 1914. The installation of the sewers was probably too late to influence very much the pellagra incidence in 1914.

In the year 1915 there were eight new cases of pellagra found on the mill property. Two of these were children who had been living for at least two years in a district sewered in March, 1914. The father of one and the mother of the other were old pellagrins. In both these

5. This number does not include Pellagrins 91 and 991 with origin in 1911 and 1913, respectively. Both of these patients apparently contracted the disease while residing in this district, but moved away before the erythema appeared.

6. This number does not include Pellagrin 868, who had resided in Spartan Mills for about twelve years, but first developed the pellagrous erythema in 1913 while away on a visit.

children the diagnosis is somewhat doubtful, for they showed an eruption on the feet only, and this eruption has never recurred. Another case was in a woman who had lived in the sewered district since November, 1914. She gave birth to a child in June, 1915, and broke out with pellagra in July, 1915. Previous to November, 1914, she had lived in an unsewered mill in next-door relationship to a pellagrin. Another patient, Pellagrin 1282, was a feeble-minded woman, who denied all symptoms of pellagra, but showed a typical eruption in August, 1915. She may have had the disease previously, but has been recorded as a 1915 case. She lived with her mother, Pellagrin 940, in the sewered house since October, 1914, having previously lived in the unsewered section, where her mother contracted the disease in the summer of 1914. Another woman, Pellagrin 1336, had lived in the mill village since May, 1913, and suffered her first attack of pellagra in April, 1915. In February, 1915, she spent a week at her father's house in the country, her mother being severely ill with some gastro-intestinal disorder at that time. Her father had been a pellagrin for several years and a sister, living at home, had her first attack in the previous summer. Pellagrin 1336, herself, developed pellagrous erythema of the hands about six weeks after her return to Spartan Mills. Another case was in a baby who came to this village in the latter part of January, 1915, and broke out with pellagra May 28, 1915. Her mother was an old pellagrin and was severely ill with a recurrent attack of the disease in April, 1915, and was committed to the State Hospital for the Insane about May 20. The house was in a filthy condition during the mother's illness. In an unscreened house next door to this one, Pellagrin 1279 had her initial attack June 15, 1915. She had lived there only since March. Before that she had lived for eighteen months in an unsewered section. Her daughter, aged 7, living with her, had been a pellagrin since 1913. The eighth patient, Pellagrin 1303, had lived in a neighboring unsewered mill village from November, 1914, to April, 1915, and she had shown indefinite symptoms of pellagra there in March, 1915. Her first erythema appeared early in June, 1915, about two months after coming to Spartan Mills.

In 1916 only two cases of pellagra are known to have appeared in the mill village. One woman, Pellagrin 1377, had her initial attack in June, 1916. She was an old resident and lived in a house at the edge of the sewered district just across the street from an unsewered house in which an old pellagrin resided. Pellagrin 1377 had borne a child in the latter part of April, 1916. The other patient, Pellagrin 1356, came to Spartan Mills in April, 1916, and developed her first erythema in that month. Previously she had been living with her daughter, Pellagrin 1167, in an unsewered house.

In this sewered district the number of new cases each year has shown a progressive diminution since 1913, being eighteen in 1914, eight in 1915 and two in 1916. The installation of the sewers could have had only a partial effect in 1914, because the connections were not completed until May of that year. In 1915 the incidence diminished very appreciably, but a number of new cases appeared among people who had moved into the mill village within a year. This influx was due to the very serious financial depression, and especially to the general depression in the cotton market from August, 1914, through 1915. Except for the two children in whom the diagnosis was doubtful, and the one woman, Pellagrin 1336, who had nursed her mother on her father's farm for a week in February, 1915, all the new pellagrins had moved within a year. In 1916 the result of the experiment is even more clearly evident. In this year only one new case appeared among the older residents on the mill property, and that was in a house at the extreme edge of the sewered district.

During the same years nine new cases of pellagra appeared in the small group of the more well-to-do population living in the adjacent partly sewered district which has been included in the survey. Three of these appeared in 1914. Pellagrin 1389, a contracting carpenter in very comfortable financial circumstances, suffered his first attack in 1914 in a house next door to pellagrins living on either side in unsewered houses. He had been living in the same house for several years. Pellagrin 940, an old woman, suffered her first attack in 1914 in a house next door to an unsewered house in which two pellagrins were living. Pellagrin 1289, a young girl, had her first attack while living with her pellagrous mother in an unsewered house. In 1915, after the general enforcement of the sanitary ordinance in regard to privies in Spartanburg City, only two new cases of pellagra appeared in this district. One was a man, Pellagrin 1314, living in an unsewered house with his wife, an old pellagrin. The other patient was a woman, Pellagrin 1285, who had moved about a good deal. She lived with her mother, Pellagrin 912, until the summer of 1914, in a sewered house just across the street from an unsewered house in which an active pellagrin resided until October, 1914. This patient, Pellagrin 1285, moved to the unsewered district outside the mill property Jan. 1, 1915, and into a house just vacated by a pellagrin. She gave birth to a child Feb. 14, 1915, and had her initial erythema in May, 1915.

In 1916 there were four new cases of pellagra in this district, three of them in one little focus in two houses immediately adjacent to a dilapidated and very dirty surface privy, which was used daily by old pellagrins, and one of them in a sewered house in which an old pellagrin resided at the time.

TABLE 2.—Pellagrins Residing in Spartan Mills in Each Year Classified According to Manifestations of the Disease and Length of Residence

Year	With Indefinite Record		Without Recurrence		With Recurrent Attack		With Initial Attack	
	Old Residents	Recent Arrivals	Old Residents	Recent Arrivals	Old Residents	Recent Arrivals	Old Residents	Recent Arrivals
1908	0	0	0	1	1	0	2	1
1909	1	1	1	0	3	1	2	3
1910	0	0	1	1	2	0	0	4
1911	2	0	2	1	8	3	13	10
1912	1	1	9	0	17	2	4	4
1913	1	1	13	1	21	5	10	14
1914	1	1	18	7	27	13	7	11
1915	1	0	22	10	26	14	3	5
1916	3	0	49	6	15	6	1	1

Table 2 shows the number of cases of pellagra known to have resided in Spartan Mills in each year from 1908 to 1916, inclusive, classified according to initial attack, recurrent attack, absence of recurrence and lack of definite record. Each of these classes has been subdivided into two groups; one group, designated as old residents, being made up of those who had been living in the village for at least a year, and a second group comprising those who had moved into the village within the year.

Table 3 shows in a similar way the pellagrins known to have resided in the surveyed adjacent district. The data of these tables are pre-

TABLE 3.—Pellagrins Residing in Houses Adjacent to Spartan Mills in Each Year Classified According to Manifestations of the Disease and Length of Residence

Year	With Indefinite Record		Without Recurrence		With Recurrent Attack		With Initial Attack	
	Old Residents	Recent Arrivals	Old Residents	Recent Arrivals	Old Residents	Recent Arrivals	Old Residents	Recent Arrivals
1908	0	0	0	0	1	0	0	0
1909	0	0	0	0	0	1	2	0
1910	0	0	0	0	3	0	0	0
1911	0	0	0	0	3	2	0	1
1912	0	0	0	0	4	3	1	2
1913	1	0	2	4	6	2	2	0
1914	1	0	2	1	2	1	2	1
1915	0	0	1	0	6	0	1	1
1916	0	0	0	2	1	4	2	2

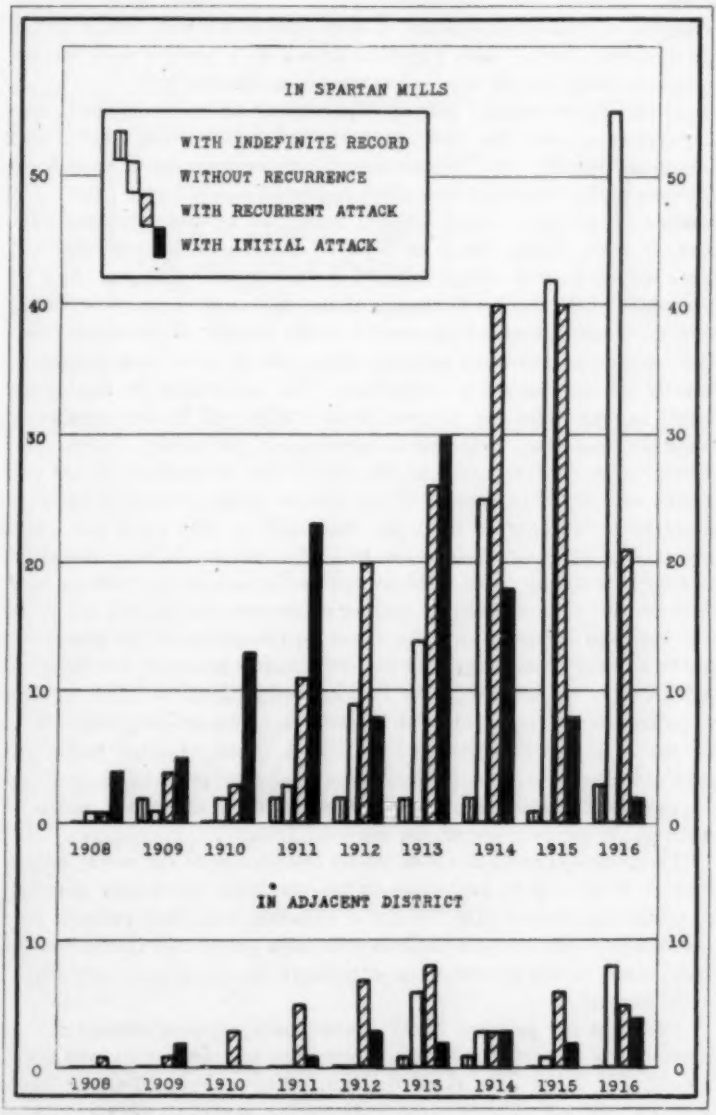


Fig. 1.—The total number of pellagrins residing in Spartan Mills and in the adjacent surveyed district in each year.

sented in graphic form in Figures 1 and 2. The former shows the total pellagrins of each class present in each year in the mill village and in the adjacent district, and Figure 2 shows in a similar way the old residents, excluding all who had moved in within the year.

In the charts one can see that the number of newly incident cases of pellagra reached the maximum in 1913, after which the number diminished rapidly. We believe that this reduction may be reasonably ascribed to the improved sanitation instituted in 1913 and 1914. The number of pellagrins who suffered recurrent attacks increased each year, to reach its maximum in 1914, in which year forty of the residents within the mill village suffered from recurrent pellagra. In 1915 the number with recurrent attacks of the disease was the same, but in 1916 there was a marked diminution in the number of recurrent cases. The amount of recurrent pellagra seems not to have been influenced directly by the change in sanitation. The diminution in this group would appear to be due in part to the falling off in the number of newly incident cases in the years immediately preceding. As we have shown in an earlier paper[7] in this series, the proportion of old pellagrins who suffer recurrence of the disease tends to diminish progressively with the lapse of time, and inasmuch as only eight new cases appeared in 1915, the recurrences in 1916 could not be very numerous unless cases dating from 1914 or before furnished the bulk of such recurrences. The diminished number of recurrences in 1916 has probably been due in part also to the increased prosperity of the population and to a considerable degree to the free dinners provided for these old pellagrins by the United States Public Health Hospital. The number of pellagrins without recurrent attack has increased progressively to the maximum of fifty-five in 1916. This shows that the pellagrous population has not been decreased especially by emigration, but that the patients have remained in the village for the most part and have outlived the active stage of the disease.

The situation brought about by the installation of the sewer system appears to be closely analogous to the condition previously observed by us[2] in the Newry Mill Village, a situation such that pellagra may continue to recur in those patients who have previously contracted the disease, but in which new cases of pellagra do not arise in any appreciable number.

The data for pellagra in the immediately adjacent district are of interest as a control study. The population of this district was about one-sixth as large as that of the mill village. From 1908 to 1913, inclusive, there had been eight instances of initial attack of pellagra

7. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: The Subsequent History of Pellagrins in Spartanburg County, S. C., Who Survived the Initial Attack, THE ARCHIVES INT. MED., 1916, **18**, 340.

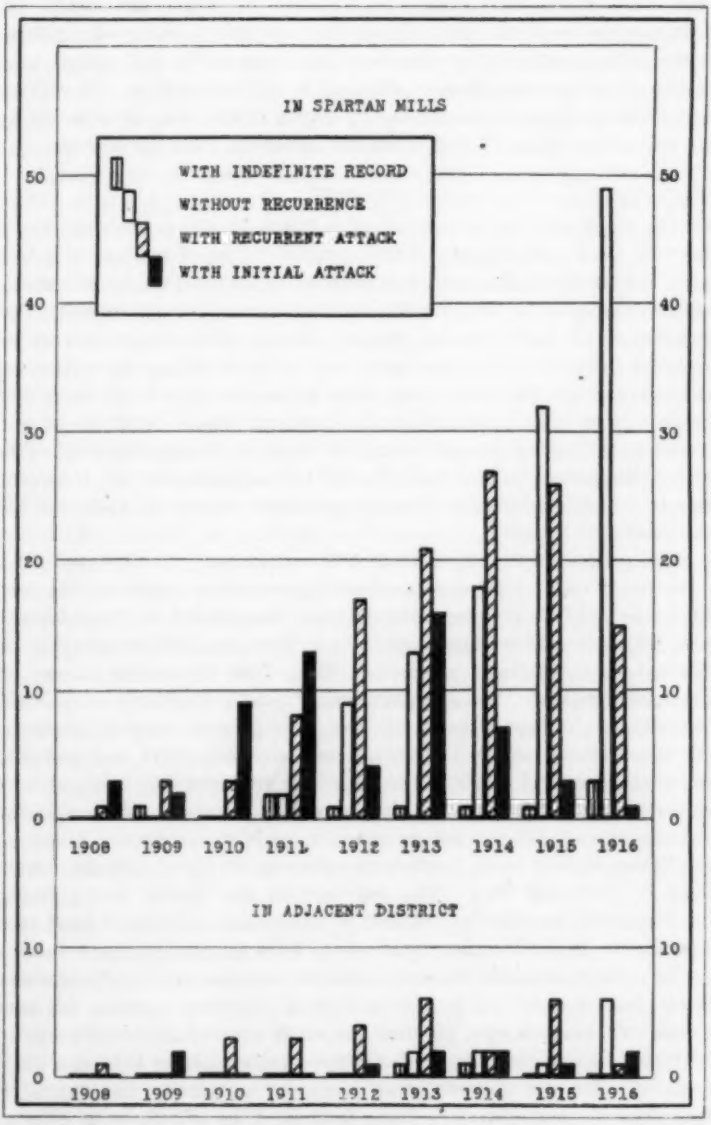


Fig. 2.—The number of pellagrins among old residents in Spartan Mills and in the adjacent surveyed district in each year.

here, while eighty-three cases had arisen in the mill village itself. In 1914 there were three new cases in this control district and eighteen in the mill village; in 1915 two here and eight in the mill village, and in 1916 four here as against only two in the mill village. It will be noted that pellagra has continued to spread in this district adjacent to the mill village since 1913 at about the same rate as it did before.

COMMENT

The diminution in new cases of pellagra in this community from thirty in 1913 to eighteen in 1914, eight in 1915 and two in 1916, has been very remarkable, and the obvious cause of this improvement would appear to be the intentional experimental factor, namely, the installation of the sewerage system. It is necessary, however, to examine critically the experiment and to give full consideration to other possible factors which may have entered into and influenced the result. Especially important in this respect would seem to be the condition of general prosperity and the possible changes in food habits of the population, for it is well known that both incident and recurrent attacks of pellagra tend to be more prevalent among the poor and ill-nourished.

The general prosperity may first be considered. In 1913 and 1914 these people were in better financial circumstances than in 1911 and 1912. In 1915 they were suffering from the general business depression, which became serious about Aug. 1, 1914, too late, however, to be effective in the pellagra season of 1914. This depression caused an influx of the poorer farming population to the mill, where work could be obtained although wages were low. The general financial condition of the population in 1915 was much worse than in 1914 and probably worse than in 1911 or 1912. In 1916 this situation had been relieved and the demand for labor elsewhere had brought about a slight increase in wages in the mill in order to retain the workers. Financial conditions in 1916 were much better than in 1915 and probably better than in 1913 and 1914. The influence of this factor is apparently manifested by the smaller number of recurrences in 1916 as compared with 1915. It is necessary, however, to keep in mind that a reduction in the number of newly incident cases in one year necessarily tends to bring about a reduction in the number of recurrent cases in the next subsequent year or two, so that the small number of recurrences in 1916 may be partly due to smaller crops of new cases in 1914 and 1915. Granting, for the moment, that increased prosperity has caused a reduction in recurrent cases from forty in 1914 and forty in 1915 to twenty-one in 1916, it is evidently quite impossible to ascribe to it the decrease in newly incident cases from thirty in 1913 to eighteen in 1914, when the recurrent cases increased from twenty-six to forty, or

the further decrease to eight incident cases in 1915 while the recurrences still remained at forty. Furthermore, in 1916 the newly incident cases were reduced almost to the vanishing point while the recurrent cases were only about 50 per cent. less than the largest number ever observed. The reduction in the incident cases cannot, therefore, be satisfactorily ascribed to the improved financial conditions.

Another factor which requires consideration is the possible change in diet of the population, dependent on educational propaganda resulting from the investigations of pellagra, and on the presence of the pellagra hospital located within this mill village. This hospital was conducted by our commission in 1913 and was taken over by the United States Public Health Service in 1914. The value of improved nutrition in the prevention and treatment of pellagra has been preached to this population by us since 1912, and since the fall of 1914 the Public Health Service has provided a free dinner for all known pellagrins who would come regularly to partake of it. This food was provided only for pellagrous individuals and not for the general population. The educational campaign has also reached especially the pellagrins, but of course to a less degree the general population. It is perhaps justifiable to credit, in part, to this campaign of dietary improvement the progressive increase since 1912 in the number of old pellagrins without recurrence present in this community and the actual reduction in recurrent attacks observed in 1916, especially the latter, because of the improved diet actually given to many of the old pellagrins. An attempt to ascribe the diminution in newly incident cases to improved dietary meets at once with difficulties of the same nature as those mentioned in the preceding paragraph. The diet has been applied directly and definitely to the old cases of the disease with the result that the recurrences have been reduced from twenty-six in 1913 to twenty-one in 1916, while among the general population, on whose diet the effect of this factor was only indirect and probably very slight, the number of incident cases of pellagra has diminished from thirty in 1913 to two in 1916.

When, therefore, the influence of these general factors is examined and measured by the behavior of the old cases of pellagra, it is found quite inadequate to explain the diminution in the number of newly incident cases of pellagra, and, therefore, quite inadequate to have influenced materially the result of the main experiment. A further light is thrown on the matter by the control group of population in the adjacent surveyed district.

The people in this district adjacent to Spartan Mills were influenced also by the general prosperity, by the educational propaganda and by the free dinners. The eight pellagrins in this district who escaped recurrence in 1916 may perhaps be reasonably credited in part to these

factors. It is, however, very significant that in spite of these general influences new cases of pellagra were as numerous as ever in 1916 in this district. In fact, more new cases occurred here in 1916 than in the enormously greater population of the mill village itself.

This experiment at Spartan Mills is, of course, only one experiment, and we realize that sweeping conclusions cannot justly be drawn from any single experiment in which various uncontrolled and unknown factors may have entered. Nevertheless, we feel justified in pointing out that the result of the experiment is fully in accord with the hypothesis announced at its inception, as a test of which it was undertaken. Furthermore, the outcome of this experiment considered together with the large mass of epidemiologic evidence, previously presented by us and confirmed by other independent observers, seems very convincing. We feel warranted in continuing to recommend most heartily the installation of sanitary systems of sewage disposal as an important means of restricting the spread of pellagra.

SUMMARY

1. Subsequent to the installation of a water carriage system of sewage disposal at Spartan Mills, the community has been transformed from a pellagra focus to a community in which pellagra no longer spreads.

2. Old cases of pellagra have continued to recur in this community, although a distinct decrease in them has occurred in the third year after the installation of the sewers.

3. The installation of sanitary systems of sewage disposal is recommended as a measure for the restriction of the spread of pellagra in the general population.

INTESTINAL EOSINOPHILIA, WITH REPORT OF A CASE*

GEORGE D. BARNETT, M.D.
SAN FRANCISCO

The occurrence of eosinophilic cells or Charcot-Leyden crystals in the mucus of stools has been occasionally reported almost ever since Ehrlich first described the eosinophil in 1879. They have been found with greatest frequency in cases of parasitic disease, especially amebiasis and hookworm disease, and in the latter condition the finding has been reported to be almost a constant one. It has also been known for a long time that they may occur in certain non-parasitic conditions, notably mucous colitis.[1] But the great variability of the intestinal eosinophilia in cases otherwise entirely similar has made the finding rather a clinical enigma than a sign of any diagnostic importance. For this reason Schmidt[2] has considered it inadvisable to attempt any grouping of cases on this basis. In his opinion eosinophils may occur in varying numbers in intestinal mucus in almost any type of colitis. In a few cases, however, where the rectum and sigmoid have been particularly involved, other investigators have attempted to establish a type of intestinal eosinophilia as a clinical entity.

Neubauer and Stäubli[3] in 1906 reported seven cases in which either eosinophils or Charcot-Leyden crystals were noted in the stools. Of these, three were cases of acute diarrhea of unknown cause, clearing up promptly under hospital care. The stools all contained Charcot-Leyden crystals, and in one case many eosinophils. No parasites or ova were found, and there was no blood eosinophilia in any of the cases. The remaining four cases were of long standing—a few months to a few years—with a history of alternating constipation and diarrhea, and with negative physical findings. All the cases occurred in young adults. In the stools were found mucus, some blood, Charcot-Leyden crystals and eosinophils; no parasites or ova. There was a distinct

* Submitted for publication Jan. 11, 1917.

* From the Medical Division of the Stanford Medical School.

1. Bäumler: Ein weiterer Fall von hochgradiger Anämie, Cor.-Bl. f. schweiz. Aerzte, 1881, **11,** 10. Nothnagel: Beiträge zur Physiologie u. Pathologie des Darms, 1884. Akerlund: Studien über Enteritis membranacea, Arch. f. Verdauungskr., 1896, **1,** 396.

2. Schmidt: Die Fäzes des Menschen, 1905, p. 86. Von Emden: Ueber eosinophile Cellen in den Darminhoud, Abstr., Zentralbl. f. inn. Med., 1903 **24,** 872.

3. Neubauer and Stäubli: Ueber eosinophile Darmerkrankungen, Münch. med. Wchnschr., 1906, **53,** 2380.

blood eosinophilia in three of the cases, in one case as high as 15 per cent., and this patient showed a marked secondary anemia. Proctoscopic examination showed a normal rectum in one case, but in the other three they found a much inflamed mucosa over which were scattered small areas of grayish exudate a few millimeters in diameter. Occasional erosions were noted, but no true ulceration. Microscopic examination of the exudate showed large numbers of eosinophilic cells. They consider the three cases with proctoscopic lesions to be instances of a clinical syndrome which they characterize as "eosinophilic proctitis," and that the condition is due to a constitutional anomaly.

Fricker[4] in 1907 reported another case occurring in a woman of 35 who had suffered from constipation her whole life until five weeks before coming to the hospital, when she began to have diarrhea, with a little blood at times. Physical examination was negative. Repeated examination of the stools showed some blood, much mucus, containing many eosinophils, and Charcot-Leyden crystals; no parasites or parasitic ova. Proctoscopy revealed a diffusely reddened rectal and sigmoid mucosa, thinly blood-streaked here and there, with a few small discrete areas of mucopurulent exudate. No blood examination was made. Fricker considers the case to be entirely similar to those reported by Neubauer and Stäubli. He also reports another case of intestinal eosinophilia in a child of 2½ years, with periodic diarrhea, without apparent cause. During one of these attacks the stools contained many small masses of pus the cells of which were mostly eosinophilic. The ova of trichuris trichiura were also found, and this parasite was considered to be etiologic.

Komarowsky[5] in 1910 reported two cases with diarrhea lasting several months. Physical findings were unimportant. The stools contained some blood and a moderate amount of pus, composed almost entirely of eosinophils. There was no increase in blood eosinophils in either case. The proctoscope in one case showed an edematous mucosa, somewhat eroded, with a few islands of loose mucopurulent exudate; in the other case there was a thick mucopurulent exudate throughout the ampulla recti.

Wiener[6] in 1912 searched for eosinophils in the mucus of seventeen cases of chronic proctitis. They were present in varying amount in seven of the cases, but were not associated with characteristic proctoscopic findings. The blood eosinophils were above 5 per cent. in only

4. Fricker: Ueber zwei Fälle von Darmeosinophilie, München. med. Wchnschr., 1907, **54**, 260.

5. Komarowsky: Ueber lokale Eosinophilie und eosinophile Darmerkrankungen, Arch. f. Verdauungskr., 1910, **16**, 74.

6. Wiener: Ueber Eosinophilie des Darmschleims, Berl. klin. Wchnschr., 1912, p. 258.

two of the cases, and were highest (8 per cent.) in the case having the greatest number of eosinophils in the mucus.

Our attention has recently been drawn to the subject by the following case in the medical wards of Lane Hospital.

REPORT OF CASE

History.—G. F., Italian cook, aged 40, entered the hospital Aug. 21, 1916, complaining of pain in the right side of the back, and alternating constipation and diarrhea. The family history was unimportant. He had had probable pleurisy ten years previously, with cough and night sweats; is usually moderately constipated; for the previous five years he had had occasional pain in the right back, at times sharp, and increased by exercise.

The previous few months he had had occasional attacks of diarrhea alternating with constipation. During the attacks of diarrhea the bowels moved five or six times a day, and he frequently noticed masses of mucus in the stool, and at times blood.

Examination.—Examination on admission showed a well-nourished man of good color; heart and lung findings normal; spleen just palpable; nothing otherwise abnormal in abdomen; prostate small, tender; many pus cells in prostatic fluid. Urine: specific gravity 1.020, no albumin or casts. Red blood count 3,970,000; hemoglobin 50 per cent. Dare; white blood count 8,500: polymorphonuclears, 28 per cent.; lymphocytes, 20 per cent.; large mononuclears, 4 per cent.; eosinophils, 47 per cent. A stool following castor oil contained much mucus and red blood. Microscopically a very few ova of trichuris trichiura were found after extensive search with special methods. Wassermann negative. The proctoscope inserted 23 cm. showed the mucous membrane of the rectum everywhere covered with glairy mucus, pus and bright red blood. No areas of ulceration were seen. Smears of the pus showed a large percentage of eosinophils. No Charcot-Leyden crystals were seen. A small bit of necrotic tissue found in the stools was sectioned, and showed a chronic inflammation, with large numbers of eosinophils in the mucosa and submucosa.

The patient remained in the hospital for about one week, with little change in his condition, and has since been lost sight of.

This case falls readily into the group of intestinal eosinophilia with definite proctoscopic findings, but differs from the type of eosinophilic proctitis reported by other observers mainly in the marked blood eosinophilia, and in the finding of trichuris ova in the stools. With regard to the latter, inasmuch as there was apparently a very mild infection with this parasite, and as it is not known to produce rectal lesions or such a degree of blood eosinophilia, we are not inclined to attach great importance to the finding, although, as already noted, trichuris was considered to be causative in one of Fricker's cases.

Some light has perhaps been shed on the etiology of this condition, and on the question of eosinophilia in general, by the recent studies of the relation of eosinophilia to the anaphylactic state. It has long been recognized that there is a clinical relationship between asthma, hayfever, certain skin affections, and the so-called neurotic bowel conditions characterized by the passage of large amounts of mucus. The so-called exudative diathesis, as outlined by Czerny and amplified by

Strümpell and others,[7] includes this group of conditions, and with the rise of the conception of anaphylaxis and its application to clinical matters, the view has become more and more prevalent that these conditions may be due to the effects of parenteral protein.[8] And since they are all frequently associated with an eosinophilia, it was reasonable to suspect that eosinophilia might be one of the manifestations of anaphylaxis. It has been known for many years that eosinophilia occurs at times following the injection of tuberculin[9] and of therapeutic serums,[10] but only recently have attempts been made experimentally to relate eosinphilia with anaphylaxis.

Schlect[11] produced anaphylactic shock in experimental animals, and reported marked increase in blood eosinophils in the animals surviving the shock. He also reported eosinophilia following daily injections of protein. Confirmations of this work have been reported by Schittenhelm,[12] Weinberg and Seguin,[13] and in this country by Herrick,[14] although since the latter worked with ascaris extracts, the rôle of anaphylaxis is perhaps not so clear. If we can accept the reported experimental results of these investigators, certainly Herrick's remark is conservative, that "it is tempting to conclude that hypereosinophilia is the result of sensitization to alien protein." In connection with the subject of intestinal eosinophilia, the statement of Schlecht and Schwenker,[15] that the anaphylactic bowel in the dog shows an intense local eosinophilia, is of interest. These experiments clearly suggest the possibility that both the local and blood eosinophilia in patients such as ours may be due to the parenteral digestion of protein by the patient, though we have no knowledge of the nature or portal of entry of such protein.

Sacramento and Webster Streets.

---

7. Czerny: Die exsudative Diathese, Jahrb. f. Kinderh., 1905, **61,** 199. Strümpell: Ueber das Asthma bronchiale und seine Beziehungen zur sogenannten exsudativen Diathese, Med. Klin., 1910, p. 889.

8. Meltzer, S. J.: Bronchial Asthma as a Phenomenon of Anaphylaxis, Jour. Am. Med. Assn., 1910, **55,** 1021.

9. Zappert: Ueber das Vorkommen der eosinophilen Zellen im menschlichen Blute, Ztschr. f. klin. Med., 1893, **23,** 227.

10. Schlecht: Ueber die Einwirkung von Serum-Injectionen auf die Eosinophilen und Mastzellen, Deutsch. Arch. f. klin. Med., 1910, **98,** 308.

11. Schlecht: Ueber experimentelle Eosinophilie nach parenteraler Zufuhr artfremden Eiweisses, Arch. f. exper. Physiol. u. Pathol., 1911, **67,** 137.

12. Schittenhelm: Weichardt u. Grisshammer. Eiweissumsatz und Ueberempfindlichkeit, Ztschr. f. exper. Path. u. Therap., 1912, **10,** 412. Ahl and Schittenhelm: Ueber experimentelle Eosinophilie nach parenteraler Zufuhr verschiedener Eiweissstoffe, Ztschr. f. d. ges. exper. Med., 1913, p. 111.

13. Weinberg and Seguin: Recherches biologiques sur l'eosinophilie, Ann. de l'Inst. Pasteur, 1914, **28,** 470.

14. Herrick: Experimental eosinophilia with an Extract of an Animal Parasite, THE ARCHIVES INT. MED., 1913, **11,** 165.

15. Schlecht and Schwenker: Ueber lokale Eosinophilie in den Bronchien beim anaphylaktischen Meerschweinchen, Arch. f. exper. Physiol. u. Pathol., 1912, **68,** 163.

THE SIGNIFICANCE OF EMBRYONAL FAT CELLS IN CERTAIN PATHOLOGIC CONDITIONS*

DOUGLAS SYMMERS, M.D.
AND
ALEXANDER FRASER, M.D.
NEW YORK

There are two outstanding theories concerning the histogenesis of the fat cell — one, that it is a cell set apart in early life for the specific purpose of producing fat, primitive fat organs, so-called, being found in various localities in the form of small groups of stellate or spindle cells richly permeated by capillary vessels. The cytoplasm of the primitive fat cell is finely granular and stains pinkish with eosin. As development proceeds the cell accumulates fat granules which fuse into globular shape, the cell itself becomes polygonal, then spherical in outline, the nucleus is peripherally displaced and finally compressed against the cell membrane, and the cytoplasm is reduced to a minimum. The other theory accounts for the origin of the fat cell on the basis of metaplasia of the fibroblast with the accumulation of fat within its body, and it is assumed that the fibroblast, when it fails to take on the specialized function of the fat cell, follows its natural inclination and develops into connective tissue.

It appears to us to be probable that both methods of cellular lipogenesis are effective, as shown by the fact that in certain pathologic conditions the primordial fat organs are noticeably increased in size, due to hyperplasia of their cellular constituents, and that, inversely, in many cachectic subjects, particularly in the epicardial and perirenal tissues, the fat disappears from the cell and the cytoplasm is replaced by serous fluid, the cell reverting to the polygonal form of the embryonal unit — the so-called serous atrophy of fat. Identical reversionary changes may be produced in the cervical fat tissues of the pig by prolonged fat starvation,[1] but, if the animal be given carbohydrate, the fat is replaced in the cell body. In other circumstances, notably in chronic productive inflammatory lesions attended by overproduction of fibroblasts, the transformation of young connective tissue elements into cells indistinguishable from those of the primitive fat organs can actually be observed in suitably stained microscopic preparations.

---

* Submitted for publication Dec. 16, 1916.

* From the Pathologic Laboratories, University and Bellevue Hospital Medical College.

1. Herter: Jour. Exper. Med., 1898, **3**, 293.

Up to, and even for a considerable period after birth, small groups of fat cells, collectively known as primitive fat organs, are to be found over a wide distribution. They may be so minute as to escape detection by the unaided eye, or they may be apparent in the form of small, rounded or oval, stellate, or otherwise angulated bodies whose color, depending on the degree of vascularity, varies from a yellowish-brown to a bright cherry-red. They occur with noticeable frequency around the kidneys and suprarenal capsules, in the loose connective tissues of the precordium, and in the fascial planes of the neck and interscapular

Fig. 1.—Low power photomicrograph showing islands of embryonal fat cells. From a marantic infant. The darker stained areas represent injected capillaries and the lighter stained bodies between them are embryonal fat cells with lightly stained, granular cytoplasm, and moderately chromatic nuclei.

region, but may be seen in practically any locality in the body where fat normally exists. In certain pathologic conditions, however, these collections of primitive fat cells may be increased to such an extent as to resemble a disseminated neoplasmic growth, while in the neck they have recently been mistaken for a new variety of gland belonging to the endocrine system (described later).

In the body of an infant investigated post mortem by one of us (Symmers) at the New York Hospital, embryonal fat cells occurred in enormous numbers, and were so distributed as to suggest the pres-

ence of a new growth. The subject was a boy, aged 3 months, dead of inanition. In the loose connective tissues around the larynx, esophagus and thyroid gland, in the fascial planes between the muscles of the anterior and lateral portions of the neck, in the connective tissue between the pectoralis major and minor muscles and the coracobrachialis on the left side, in the loose tissues of the precordium, and in the parietal pleura corresponding to the lower edges of the fourth and fifth ribs on the right side, in the loose tissues immediately behind the sternum from end to end, and behind and in front of both kidneys, especially the left, was a quantity of cherry-red tissue so distributed, practically wherever found, as to form a rough lattice work made up of pea-sized, oval or rounded, glistening bodies arranged discretely or joined by strands of the same general appearance. This trellis-like distribution was particularly noticeable in the retrosternal region, in the precordium, and around the thymus gland, where it was abundant. In the neck, and between the superficial muscles of the thorax, the tissue was found in branching chains. In the connective tissue of the right pleura the tissue formed chains which lay parallel with the edges of the ribs. The tissue in the peritoneum in front of the kidneys, and in the capsules of the kidneys themselves, was arranged in a coarse network. Behind the kidneys the tissue was clumped to form thick, cord-like masses lying in the fascia of the psoas magnus muscles. In specimens fixed in formaldehyd solution the reddish bodies described could be seen breaking up into small angulated masses loosely held together by connective tissue.

Histologic examination showed the presence of innumerable small, rounded, oval, or angulated, richly cellular islands lying in a reticulum of loose connective tissue. The islands were composed of a complex network of injected capillaries, between which were groups of large polyhedral cells, with small, rounded, moderately chromatic, centrally placed nuclei, and finely granular, pinkish cytoplasm. In many of the cells sudan III showed the presence of numerous minute orange-red granules lying in the cytoplasm, while others were free.

In connection with the question of embryonal fat tissues, it is of interest to note that Pende[2] has recently described what he believes to be a new gland of internal secretion belonging to the endocrine system (glandula insularis cervicalis). He found it in children and in puppies in the form of from fifteen to twenty solid islands of cells which he assumed to be of epithelial nature and which lay in the connective tissue around the thyroid and thymus glands. The cellular islands appeared as richly vascularized, reddish bodies made up of small,

2. Pende: Arch. f. mikr. Anat., 1915, **86,** 193.

sharply defined cells of rounded or polygonal outline with a centrally placed, vesicular nucleus, and a distinct cell membrane. The cell membrane enclosed numerous small granules so closely packed as to give the cytoplasm a homogeneous appearance, the granules staining pinkish with eosin and responding to special stains for fat. Pende assumed that the granular and fatty substances in the cell body represented the visible expression of an internal secretion. It requires but a glance at the several illustrations which accompany Pende's paper to convince one that the body specifically described by him as a new member of the endocrine series is identical with the primitive fat organs.

Fig. 2.—High power photomicrograph to illustrate the histologic changes in a disease characterized by interference with the absorption of fat and the deposition of neutral fat and fatty acid crystals in the intestine, mesentery, and mesenteric lymph nodes. Note the enormous hyperplasia of embryonal fat cells. (Nodule from mesentery.)

There is a group of chronic productive inflammatory lesions occurring commonly, but not exclusively, in tissues more or less rich in fat, in which either the pre-existing fat cells undergo proliferation with the production of polygonal forms indistinguishable from the embryonal fat cells, or in which certain numbers of the fibroblastic elements participating in the inflammatory reaction undergo metaplasia into fat cells. We have encountered changes of the sort indicated in the female breast in a case of chronic interstitial mastitis, the fat cells being

arranged in islands lying between masses of dense fibrous tissue. In a chronic productive lesion of the gallbladder and another of the intestine, embryonal fat cells were found widely distributed through the interstitial tissues in the form of narrow strands or as small groups. In a case of chronic interstitial nephritis, the intertubular connective tissues were richly infiltrated, the embryonal fat cells evidently originating in the pelvis and migrating toward the cortex. Like embryonal fat cells elsewhere, they presented an appearance suggestive of infiltrating hypernephroma cells, but the absence of such a growth excluded this possibility. In two chronic productive inflammatory lesions of the mesentery, embryonal fat cells were found diffusely distributed through the connective tissues, and, in a case of tuberculosis of the knee joint, the marrow of the corresponding femur was found to be extensively invaded.

The histologic study of embryonal fat cells in chronic productive inflammatory lesions shows that these cells are migratory. The phenomenon of migration of definitely formed fat cells among alien tissues is obviously different from the infiltration of extracellular fat globules along the line of least resistance, and, in fact, partakes of the nature of an invasive process. It is also exemplified by lipomata composed of embryonal fat cells that display a disposition to invade surrounding tissues, so that a tumor which, in ordinary circumstances, pursues a benign course, is thus diverted in the direction of malignancy. Mallory[3] mentions such a case, and, in the pathologic laboratories at Bellevue Hospital, we have recently encountered a lipoma in the arm of a 16-year-old girl that was composed of embryonal cells in various stages of development. Still another example of the migratory property of embryonal fat cells is to be found in the pathologic histology of the intestine, mesentery and mesenteric lymph nodes in a case recorded by Whipple.[4] The patient was the subject of a disease characterized, clinically, by gradual loss of weight and strength, by the presence of a great abundance of neutral fat and fatty acids in the stools, by vague signs referable to the abdomen, and by a variety of fugitive arthritis involving multiple joints. With the exception of the joints, which could not be investigated post mortem, the anatomic changes were limited to that part of the body mechanism which has to do with the absorption of fats, namely, the small intestine and its lymphatic drainage system. The intestinal villi were enlarged on account of extensive deposits in the lymph spaces of neutral fats and fatty acids, together with infiltration of the interglandular connective

3. Mallory: Principles of Pathological Histology, 1914, Ed. 1, p. 207.
4. Whipple: Bull. Johns Hopkins Hosp., 1907, **18,** 382.

tissues by mononuclear cells morphologically identical with embryonal fat cells, and by the presence of multinuclear giant cells. The submucous connective tissues and the mesenteric nodes were similarly affected. The latter structures presented, in addition, microscopic changes which Whipple interpreted as a chronic productive inflammatory process.

As far as we have been able to determine, the case described by Whipple is the only one of the sort in the literature of medicine. What we believe to be a case of the same type, however, recently came under our observation.

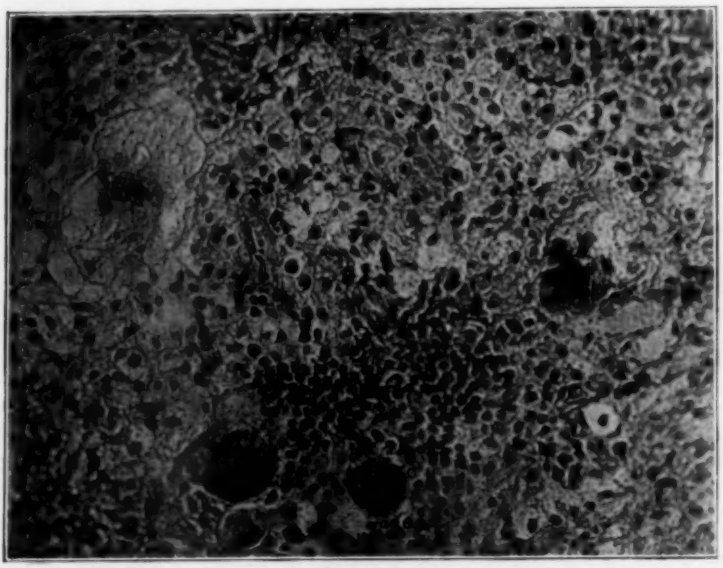


Fig. 3.—Same disease as represented by Figure 2. At the left is a giant cell due to fusion of embryonal fat cells. The other giant cells are of the Langhans type. Note the profusion of embryonal fat cells throughout the field.

The patient, a woman aged 43, was operated on by Dr. George D. Stewart, who found a large, lobulated mass in the region of the pancreas that resembled a group of tuberculous lymph nodes, and exuded a milky fluid on being incised. There were no clinical symptoms referable to disturbances in the absorption of fat, the stools being free. The patient is still under observation, however, and is being watched for the development of manifestations of the sort indicated. The pathologic histology of a small nodule removed from the region of the pancreas at the time of operation, revealed changes in complete agreement with those described by Whipple in the intestine, mesentery, and mesenteric nodes, and illustrated in his paper.

The framework of the nodule was composed of irregularly scattered trabeculae of connective tissue, between which were vast numbers of large, rounded,

oval, or polygonal cells with a distinct limiting membrane, a fairly richly chromatic, centrally placed nucleus, and finely reticulated or granular, pale, poorly staining cytoplasm. In sudan III preparations practically every one of these cells revealed innumerable fat granules in the cytoplasm and overrunning the nucleus. Here and there were a few apparently well developed, fat-free fibroblasts, and an occasional lymphomatous focus. Scattered among the cells were considerable numbers of large fat vacuoles. In many instances the cells in the immediate vicinity of the vacuoles showed no changes beyond slight condensation of their cytoplasm; in other cases the vacuoles were rimmed by multinucleated giant cells, obviously derived from fusion of two or more embryonal fat cells. In occasional instances there were isolated giant cells with an unusually distinct cell membrane, a large amount of pale, finely granular or reticulated cytoplasm, and a half dozen or more well-formed, rounded nuclei, each of which was surrounded by a distinct membrane enclosing, in many instances, a nucleolus. Fat granules were abundant. Mitotic figures could not be found, but evidences of direct nuclear division were visible, and this was apparently the method of nuclear cleavage. The prevailing giant cell, however, was a more or less acceptable counterfeit of the Langhans cell, and was provided with dense, reddish-staining cytoplasm, and multiple, richly chromatic, rounded or oval, well-formed but small nuclei. The cell was practically always built round a fat particle.

Special stains for tubercle bacilli, and Levaditi and Gram preparations were negative.

The histologic changes just enumerated are unique, and occur in no other condition with which we are acquainted. In Whipple's case they were interpreted as a chronic productive inflammatory process — a foreign body granuloma. For our own part, we recognize the probability of the correctness of this view, but are nevertheless impressed by the possibility that the lesion is capable of malignant transformation. In the latter event the growth would constitute a new variety of malignant connective tissue tumor, namely, an embryonal cell liposarcoma or malignant lipoblastoma. The exact nature of the process, however, must remain undetermined until other cases of the same sort have been subjected to detailed investigation.

A phase in the histology of embryonal fat tissues that does not appear to us to have been sufficiently emphasized is to be found in the form of the multinucleated giant cells, which occur in at least three varieties, first, as fusion cells around, or independent of, foreign particles, such as globules of fat; second, as giant cells due to division of the nucleus without corresponding changes in the cell body. This form appears to bear no relationship to the presence of foreign bodies in the tissues, but is best interpreted as an abortive attempt at regeneration; the third variety is a more or less acceptable counterfeit of the Langhans giant cell, and is almost invariably built around particles of fat, cholesterin, or fatty acid crystals, or around stellate bodies of indeterminate nature. The occurrence of stellate inclusions in giant cells was first described by Ris[5] in the walls of an omental cyst. They

5. Ris: Beitr. z. klin. Chir., 1893, **10,** 423.

have also been detected by Wolbach[6] in the lung, lymph nodes, spleen and liver, by Vogel[7] in a case of obliterating capillary bronchitis, by Iwanzoff[8] in a myomatous uterus, by Mallory[9] in the giant cells of leprosy, and by Wood[10] in a granulomatous lesion of the face following the injection of paraffin for cosmetic purposes. The radiate bodies in question have been variously interpreted as disintegrated elastic tissue, parasitic inclusions, astropheres, fibrinoid bodies, etc. We have recently had occasion to study changes in the fat cells of a regressing corpus

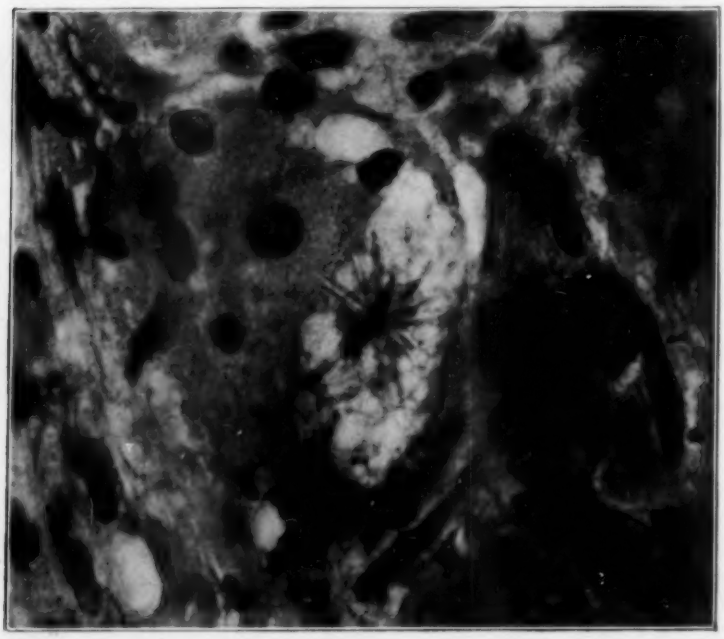


Fig. 4.—Oil immersion photomicrograph showing spiculated body (fatty acid crystal) in a giant cell of a regressing corpus luteum.

luteum attended by the formation of enormous numbers of giant cells, some of which were arranged around cholesterin crystals, others enclosing a single star-shaped body in the cytoplasm. The shape of these inclusions, and their occurrence in degenerate cells rich in fat, together with the presence in neighboring giant cells of lipoids in the

6. Wolbach: Jour. Med. Research, New Series, 1911, **19,** 243.
7. Vogel: Virchows Arch. f. path. Anat., 1911, **206,** 157.
8. Iwanzoff: Beitr. z. path. Anat., 1912, **52,** 202.
9. Mallory: Loc. cit., Note 3, p. 303.
10. Wood: Proc. New York Path. Soc., New Series, 1915, No. 5, p. 63.

form of cholesterin, incline us to the view that the stellate bodies in the regressing corpus luteum bear a definite relationship to the disintegration of fats, and are most probably of the nature of fatty acid crystals.

CONCLUSIONS

The study of embryonal fat cells in certain pathologic conditions suggests the following conclusions:

1. The histogenesis of fat cells is brought about in two ways; first, in the form of connective tissue cells set apart in embryonal life for the specific purpose of producing fat, and, second, as the result of metaplasia of fibroblasts with the accumulation of fat in the cytoplasm and the assumption by the cell of the polygonal form of the embryonal unit.

2. There is a condition in marantic infants attended by such extensive hyperplasia of the so-called primitive fat organs as to resemble a new growth. The fat bodies are cherry-red in color and are composed of embryonal fat cells and a complex system of intercommunicating capillaries. The bodies may be found wherever fat tissues normally exist, but are particularly numerous in the connective tissue planes of the neck and chest and around the adrenals and kidneys.

3. The glandula insularis cervicalis of Pende, recently described as a new member of the endocrine series, is identical in structure and function with the embryonal fat organs.

4. There is a group of chronic productive inflammatory lesions and a variety of lipoma attended by marked hyperplasia of embryonal fat cells in which these cells not infrequently display a distinct disposition to migrate into alien tissues. Moreover, there is a disease of the fat absorption apparatus characterized, histologically, by neutral fats and fatty acids in the lymph spaces of the intestine, mesentery and mesenteric lymph nodes, the tissues showing, in addition, extensive hyperplasia of embryonal fat cells and the presence of foreign body giant cells. (Whipple, Symmers and Fraser.) The histology is indicative of a chronic productive inflammatory process attended by such extensive hyperplasia of embryonal fat cells as to suggest transformation into a sarcoma (embryonal cell liposarcoma, malignant lipoblastoma).

5. Embryonal fat cells are phagocytic, and may form multinucleated giant cells around fat globules, cholesterin crystals, and the like. In other circumstances the cell, in attempting to divide, forms giant cells by repeated cleavage of the nucleus without corresponding changes in the cell body. Giant forms resulting from fusion of embryonal fat

cells also occur. In all of these varieties the cytoplasm reveals fat granules in abundance.

6. The giant cells occasionally encountered in the tissues of the regressing corpus luteum are built round foreign bodies in the form of cholesterin crystals, and the stellate radiations sometimes to be observed in the cytoplasm are probably fatty acid crystals due to disintegration of the fat cells of the part.

We are indebted to Dr. John E. McWhorter for the photomicrographs.

Twenty-Sixth Street and First Avenue.

EXPERIMENTAL APPENDICITIS *

J. W. McMEANS, M.D.
NEW YORK

Although appendicitis has long been definitely recognized as a clinical entity, there is at the present time no unity of opinion among the various investigators as to its pathogenesis. Most authors agree, however, that infection is an important factor in its production. One finds a variety of predisposing factors described as favoring the infection, but there is a disagreement as to the mode of entrance of the offending organisms into the tissue of the appendix.

Aschoff[1] has maintained that the disease has an enterogenous origin, while Kretz[2] has endeavored to demonstrate the localization of organisms in the follicular apparatus of the appendix by way of the blood stream, gaining entrance thereto, particularly, from the tonsils. The latter investigator was of the opinion that the streptococcus is the exciting cause, as he could demonstrate gram-positive cocci within the vessels in the submucosal follicles. Recently Rosenow,[3] who has studied the question of hematogenous origin of appendicitis, has endeavored to prove that streptococci isolated from diseased appendixes, or from the tonsils of patients suffering from appendicitis, possess certain transient, biologic characteristics which favor invasion of the appendix. This affinity he designates "organotropism." He asserts that organotropism is not possessed by organisms isolated from sources other than the disease focus or apparent atrium of infection. In order that this affinity may be preserved, it is requisite that the bacteria shall be isolated and handled in accordance with a particular bacteriologic technic. This affinity is transient and cannot be preserved through more than a limited number of generations, either on artificial cultivation or by animal passage. Rosenow also found that such an organotropism is not confined to the bacteriology of the appendix, but exists for the stomach and duodenum in ulcer, for the gallbladder in cholecystitis and for the joints in arthritis. There is no doubt that organisms on gaining entrance to human or animal bodies grow most luxuriantly in that tissue which affords most suitable environment. In this connection one, however, cannot overlook the possibility of sensitized or particularly susceptible tissues rather than variations in the organisms. In 1901 Adrian[4] injected various organisms intravenously into rabbits and found the appendix so regularly affected that he said this organ in rabbits is a place of predilection for the localization of organisms circulating in the blood. The relation of the tonsils to certain types of infection is apparently

* Submitted for publication Nov. 2, 1916.

* From Cornell University, Surgical Division, and the Pathological Department of Bellevue Hospital.

1. Aschoff: Verhandl. d. deutsch. path. Gesellsch., 1904, **7,** 246; ibid., 1906, **10,** 234; ibid., 1907, **11,** 313. Die Würmfortzatzentzündungen, Jena, 1908.

2. Kretz: Verhandl. d. deutsch. path. Gesellsch., 1906, **10,** 229; ibid., 1907, **11,** 309; ibid., 1910, **14,** 144; Ztschr. f. Heilk., 1907, **28,** 151; Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, **17,** 1.

3. Rosenow: Jour. Infect. Dis., 1914, **14,** 61; ibid., 1915, **17,** 240; ibid., 1916, **18,** 383.

4. Adrian: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1901, **7,** 407.

well established at the present time. It is not conceivable, however, that these organs have such a varied property that they are able to impart peculiar characters to organisms whereby an individual bacterium may possess different affinities at several distinct periods.

In view of the widespread lesions observed in human bacteremia, and with a desire to obtain more direct information on this subject, we decided to study the effects on rabbits of the intravenous injection of micro-organisms derived from several sources. At this time we wish to describe at length the appendiceal lesions observed, reserving the general description of the bacteremia produced for a later communication.

Material for this work was obtained from appendixes, from the tonsils of patients having appendicitis, from several pairs of tonsils and adenoid tissue removed in the children's clinic, from tonsils of fracture patients otherwise apparently healthy, and from pus of an infected hand. Among the appendixes there were included two normal appendixes, two acute ulcerative appendixes, three acute gangrenous appendixes (two with concretion and perforation), three chronic appendixes, peritoneal fluid in one case of appendicitis, and pus from an abscess in the abdominal incision following operation for acute gangrenous appendicitis.

TECHNIC

All cultures from the appendixes were made from the mucosal surface after opening them longitudinally under sterile precautions. Where the mucosa presented macroscopical lesions the organ was first washed in running sterile salt solution, after which material was scraped from the base of the diseased area. In the case of the perforated organs, cultures were made from the borders of the opening. The normal appendixes were ground up in a sterile mortar with sterile white sand after the organs were thoroughly washed. The tonsils studied consisted of those from five of the patients having appendicitis and those of thirteen patients not suffering with this disease; of the latter group, ten were from patients with fractures but otherwise well, while the remaining three consisted of tonsils removed from children affected with chronic tonsillitis. A mass of adenoid tissue from one of the latter three was also used for culture. Where the tonsils were removed, and likewise in the case of the adenoids, the entire tissue was ground up in a sterile mortar with sterile white sand. Cultures from the tonsils of the appendix patients, and also from the fracture patients, were made by boring sterile swabs into the crypts of the organs. The material was in each case inoculated into 150 c.c. of dextrose serum broth. The serum broth was prepared according to the method described by Holman.[5] During the first part of the work 1 per cent. of dextrose was used, while this was later changed to two-tenths per cent.; the only appreciable difference seemed to be that more luxuriant growths occurred in the serum broth containing the stronger percentage of the carbohydrate. These cultures were incubated at 37 C. for twenty-four hours, when the flask was vigorously shaken, the fluid placed in sterile 50 c.c. tubes and centrifugalized at 3,000 revolutions for about fifteen minutes, until the supernatant fluid was perfectly clear. The sediment was then collected and suspended in 10 c.c. of sterile salt solution, whereby each cubic centimeter of the suspended sediment represented 15 c.c. of the original growth, except when the

5. Holman: Jour. Infect. Dis., 1914, **15**, 209, 293.

entire sediment was injected into the ear vein in one dose, in which case it was taken up in 5 c.c. of saline. The majority of the animals received doses varying from 15 to 75 c.c. of the original growth. Before injection plain human blood agar streak plates were made and the nature of the organisms in the emulsion determined.

The relation between dosage and effect was at times inconstant. Rabbits injected with equal doses of the same suspension would show one animal living and the other dead at the end of twenty-four hours.

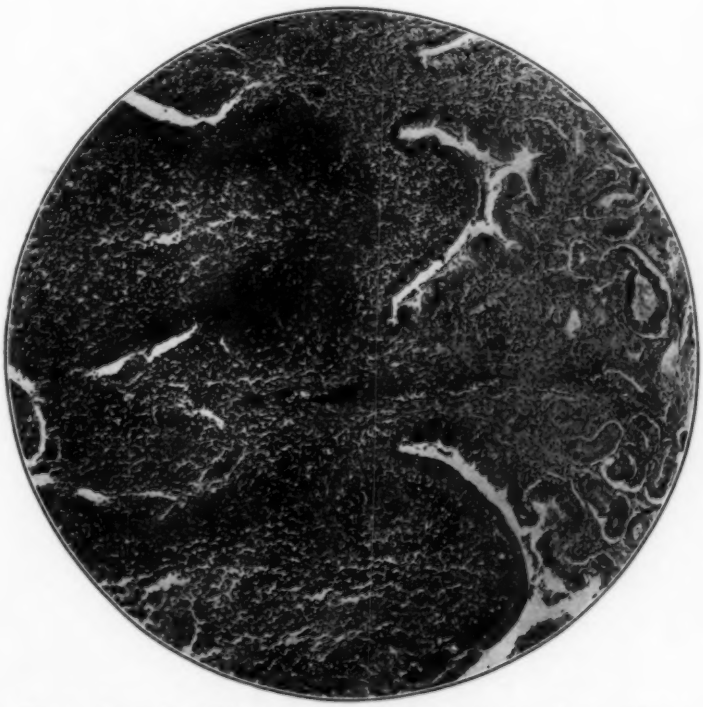


Fig. 1.—Appendix, Rabbit 75, showing marked hemorrhage into and between the follicles.

Again, on several occasions, an animal receiving a dose of 75 c.c. survived, while two receiving 30 c.c. and 45 c.c., respectively, died. From this there appeared to be an individual variation in resistance among the rabbits, so that in some of the animals which received a smaller dose there was developed a severe bacteremia with many lesions, while another rabbit, inoculated with a larger dose of the same material, when killed revealed but few alterations in its organs. Although this event was not the rule, these facts were definitely observed and should

be considered as very important when interpreting the results obtained in animal experimentation. This is a matter worthy of the serious attention of all workers in this field.

TONSILS IN APPENDIX CASES (TABLE 1)

Some of the experiments consisted of the inoculation into the ear vein of the mixed culture, the nature of the organisms given being

TABLE 1.—DATA CONCERNING THE—

Case	Source	Organisms	Rabbit No.	Rabbits Injected	Appendix	Skin	Lung	Stomach	Heart	Thymus
66	Tonsil (chronic appendicitis) (Case 67)	Staph. aureus; B. xerosis	56	1	1	1	1	...	1	1
69	Tonsil (acute gangrenous appendicitis) (Case 69)	Staph. aureus; Staph. albus	61	1	1	...	1	1	1	1
		S. pyogenes-vulgaris (append., Rabbit 61)	74	1						
71	Tonsil (acute ulcerative appendicitis) (Case 70) See Case 71 (Table 2) for detail	S. salivarius; Staph. albus	64	1	1	1	1	1	1	...
		S. salivarius (knee, Rabbit 64) into lumen	78	1	1					
		S. salivarius (into appendix artery)	79, 83, 84, 85	4	4	1	3	3	2	1
		S. salivarius.....	80, 90, 91, 92	4	...	3	2	1	2	...
		S. salivarius.....	43, 50, 82, 88, 104, 105	6	2	3	2	3	2	2
		S. salivarius (peritoneum, Rabbit 83)	119, 120, 121	3	1	3	...	3	...	1
		S. salivarius (periarticular, Rabbit 43)	122, 123, 124	3	1	3	3	2	1	2
		S. salivarius.....	125, 126, 127	3	1	3	...	...	1	1
73	Tonsil (chronic appendicitis) (Case 72)	S. mitis; Staph. albus	68	1	...	...	1	...	...	...
87	Tonsil.....	S. subacidus; Staph. albus	130, 131, 132, 133	4	2	3	2	2	1	3
		S. pyogenes-vulgaris (knee, Rabbit 130)	160, 161	2	1					
5	Totals.....	.....	.....	35	16	21	16	16	12	12

determined by previous plating. On the other hand, some organisms, particularly streptococci, were carried through several animal passages and showed interesting deviations in the frequency with which the different organs were attacked. To determine whether or not the repeated cultivation of an organism on artificial mediums or its passage through animals had any influence on the power of attacking the

appendix, we selected material from the tonsils of a patient suffering with acute ulcerative appendicitis and cultured it in the manner described. The streptococcus isolated from this case, B-71-16, produced slightly raised, glassy colonies with distinct greening on plain blood agar, which later exhibited some browning. To determine its power of ferment production, the organism was tested against lactose, mannite, salicin and inulin in serum broth as described by Holman,

—Tonsils in Appendix Cases

Duodenum	Joint	Small Intestine	Periarticular	Brain	Endocarditis	Kidney	Cord	Cecum	Pericardium	Muscle	Pleura	Gall Bladder	Liver	Large Bowel	Eye
1	...	1	...	...	...	1	...	...	1						
...	...	1													
1	1	...	...	...	1	1	...	...	1	...	1				
...	1	2	...	...	...	...	...	2	...	...	1	1			
...	...	...	...	...	...	1	...	...	...	...	...	1			
2	2	1	2	...	1	1	...	1	1	2	...	...	2	1	
2	...	...	1	2	1	...	1	...	...	1	...	...	...	...	1
2	2	...	1	...	1	...	1								
2	...	...	...	3	...	...	2								
...	...	1													
1	4	...	1												
11	10	6	5	5	4	4	4	3	3	3	2	2	2	1	1

and was found to attack only lactose, the observation being continued for fourteen days. Morphologically, the organism was seen in hanging drop preparation from the lactose serum broth to occur in pairs and pairs in chains of ten and more round or slightly elongated cocci. The organism was gram-positive. It conformed, therefore, in all particulars to the *Streptococcus salivarius*. All of the streptococci for this work

were studied in this manner at all stages of the different experiments. Following the isolation of this streptococcus from the original tonsil (Case B-71-16) and after animal passage, the organisms were cultured on plain 5 per cent. human blood agar, transfers being made to new blood agar slants each time a subculture was made. The sediment of the original growth was suspended in 5 c.c. of normal saline solution and inoculated into the ear vein of Rabbit 64. The animal died two days later and at necropsy the appendix exhibited numerous pinpoint

Fig. 2.—Appendix, Rabbit 84, showing two follicles almost completely replaced by hemorrhage, which also extends to the surface of the mucosa.

red areas in the mucosa of its middle portion together with hemorrhages into the skin, endocardium, lung, stomach, duodenum, pleura and pericardium, with a vegetative endocarditis involving the tricuspid valve and lesions observed as small white dots in the heart muscle and kidney. From the heart blood and knee joints a *S. salivarius* was isolated. The material with which Rabbit 64 was injected came to the laboratory January 16, and on culture showed a *S. salivarius* and *Staphylococcus albus.*

On January 28 two rabbits, 78 and 79, inoculated with small doses of the *S. salivarius* respectively into the lumen of the appendix and artery of the organ, presented only local reaction, while Rabbit 80 received the growth from 150 c.c. into the ear vein, and when killed six days later showed no alterations in its organs. Three rabbits, 83, 84 and 85, injected January 31 into the appendiceal artery with small doses, not only presented a local appendicitis, but also lesions in other organs, thus demonstrating that the streptococcus, although given every opportunity, did not tend to produce lesions solely in the appendix. A *S. salivarius* isolated from the knee joint of Rabbit 83 and carried along on plain blood agar until February 15, was again grown in 150 c.c. of dextrose serum broth and inoculated in divided doses into the ear veins of Rabbits 43, 59 and 82. Two of these animals, 43 and 59, which received, respectively, 30 and 45 c.c., died, and at necropsy showed lesions in the appendix and many other organs, while Rabbit 82, which received 75 c.c., lived, and when killed two days later showed lesions only in the stomach and lung. Again, on February 19, three rabbits (119, 120 and 121) injected, respectively, with 40, 60 and 50 c.c. of a *S. salivarius* from the peritoneum of Rabbit 83, showed the appendix affected only in Rabbit 120. Three rabbits (122, 123 and 124) received, respectively, 30, 45 and 75 c.c. of a *S. salivarius,* isolated from a hemorrhage about the knee joints of Rabbit 43, and showed the appendix affected in but one animal, Rabbit 123. February 24, three rabbits (125, 126 and 127) inoculated, respectively, with 30, 45 and 75 c.c. of a *S. salivarius* from the blood of Rabbit 43, revealed the appendix affected in one only, rabbit 127. The details of these experiments are presented in Table 2, Case 71.

From the results described it will be noted that the rabbits' appendixes were affected in each of four groups with a *S. salivarius* derived from a source other than the appendix; that is, from the knee joint, the periarticular tissues, the peritoneum or the heart blood, and that the animal receiving the largest dose in any group was not necessarily the one to exhibit changes in its appendix. Lesions in the appendix followed the intravenous injection of the streptococcus from each of the sources named. Another interesting feature displayed by this streptococcus during the time it was studied consisted in the marked variation with which it attacked the different organs; even in animals injected with doses from the same subculture, no definite order of invasion was followed. That the organism apparently did not tend to lose its power of attacking the appendixes of some rabbits is demonstrated by the production of an appendiceal condition in five of twelve rabbits thirty days after the original isolation (B-71-16), only one animal passage having supervened. From the time of the first animal passage when the organism was isolated from the knee joint of Rabbit

TABLE 2.—DETAILED DATA—

No.	Date	Source	Material	Amt. C.c.	Method	Death	Date	Skin	Heart	Lung	Stomach	Duodenum	Appendix
64	1/17	Tonsil B-71-16	Mixed	150	Ear vein	Died	1/19	+	+	+	+	+	+
78	1/28	Knee joint R-64-16	S. salivarius	½	Lumen of appendix	Killed	1/30	—	—	—	—	—	+ Local
79	1/28	B-71-16	S. salivarius	1	Appendix artery	Killed	1/30	—	—	—	—	—	+ Local
80	1/28	B-71-16	S. salivarius	150	Ear vein	Killed	2/ 3	—	—	—	—	—	—
83	1/31	B-71-16	S. salivarius	½	Appendix artery	Died	2/ 2	—	+	+	+	—	+ Local
84	1/31	B-71-16	S. salivarius	1	Appendix artery	Died	2/ 1	—	—	+	+	—	+ Local
85	1/31	B-71-16	S. salivarius	1	Appendix artery	Died	2/ 1	+	+	+	+	—	+ Local
90	2/ 2	B-71-16	S. salivarius	150	Ear vein	Died	2/ 3	+	+	+	—	—	—
91	2/ 4 2/ 5	B-71-16	S. salivarius	10-10	Ear vein	Killed	2/ 7	+	—	—	—	—	—
92	2/ 4 2/ 5	B-71-16	S. salivarius	10-10	Ear vein	Died	2/ 7	+	+	+	+	—	—
104	2/14	Knee joint R-83	S. salivarius	30	Ear vein	Killed	2/15	—	+	—	+	—	—
105	2/14	Knee joint R-83	S. salivarius	75	Ear vein	Killed	2/15	+	—	—	—	—	—
88	2/14	Knee joint R-83	S. salivarius	45	Ear vein	Killed	2/15	—	—	—	—	—	—
43	2/16	Knee joint R-83	S. salivarius	30	Ear vein	Died	2/17	+	+	+	+	+	+
59	2/16	Knee joint R-83	S. salivarius	45	Ear vein	Died	2/17	+	—	—	—	+	+
82	2/16	Knee joint R-83	S. salivarius	75	Ear vein	Killed	2/18	—	—	+	+	—	—
119	2/19	Peritoneum R-83	S. salivarius	40	Ear vein	Killed	2/22	+ Also lip	—	—	+	+	—
120	2/19	Peritoneum R-83	S. salivarius	60	Ear vein	Killed	2/21	+	—	—	+	+	+
121	2/19	Peritoneum R-83	S. salivarius	50	Ear vein	Killed	2/22	+ Lip	—	—	+	—	—
122	2/22	Skin knee R-43	S. salivarius	30	Ear vein	Killed	2/23	+	—	+	—	+	—
123	2/22	Skin knee R-43	S. salivarius	45	Ear vein	Died	2/23	+	+	+	+	+	+
124	2/22	Skin knee R-43	S. salivarius	75	Ear vein	Died	2/23	+	—	+	+	—	—
125	2/24	Blood R-43	S. salivarius	30	Ear vein	Killed	2/25	+	+	—	—	+	—
126	2/24	Blood R-43	S. salivarius	45	Ear vein	Killed	2/28	+	—	—	—	—	—
127	2/24	Blood R-43	S. salivarius	75	Ear vein	Died	2/27	+	—	—	—	+	++
25	.....	.....	.....	.....	.....	.....	.....	17	9	11	13	9	11

— CONCERNING CASE 71

Small Intestine	Cecum	Large Bowel	Eye	Pleura	Gland	Muscle	Endocarditis	Pericardium	Kidney	Gallbladder	Liver	Joint	Periarticular	Brain	Cord
—	—	—	—	+	—	—	+	+	+	—	—	+	—	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	+	—	—	+	—	—	—	—	—	+	—	+	—	..	..
+	+	—	—	—	—	—	—	—	—	—	—	—	—	..	..
+	—	—	—	—	+	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	—	—	+	+	—	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	+	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	—	—	—	—	+	—	—	..	..
—	—	+	—	—	+	+	—	—	—	—	—	+	+	..	..
+	+	—	—	—	+	+	+ TO	+	+	—	—	+	+	..	..
—	—	—	—	—	—	—	—	—	—	—	—	—	—	..	..
—	—	—	—	—	—	—	+ MO	—	—	—	—	—	—	+	+
—	—	—	—	—	+	+	—	—	—	—	—	—	+	—	—
—	—	—	+	—	—	—	—	—	—	—	—	—	—	+	—
—	—	—	—	—	—	—	—	—	—	—	—	+	—	—	+
—	—	—	—	—	+	—	—	—	—	—	—	+	+	—	—
—	—	—	—	—	+	—	+ TO	—	—	—	—	—	—	—	—
—	—	—	—	—	+	—	—	—	—	—	—	—	—	+	+
—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	+
3	3	1	1	2	7	3	4	2	3	2	2	6	4	5	4

83, it was cultured for the next sixteen days on plain blood agar, and when the growth from 150 c.c. of a subculture in dextrose serum broth was inoculated into Rabbits 43, 59 and 82, the appendix was affected in two instances, Rabbits 43 and 59. Although the organism had been tried in six animals during the preceding sixteen days, the appendixes in all were unaffected. This lapse in its ability to affect the appendix

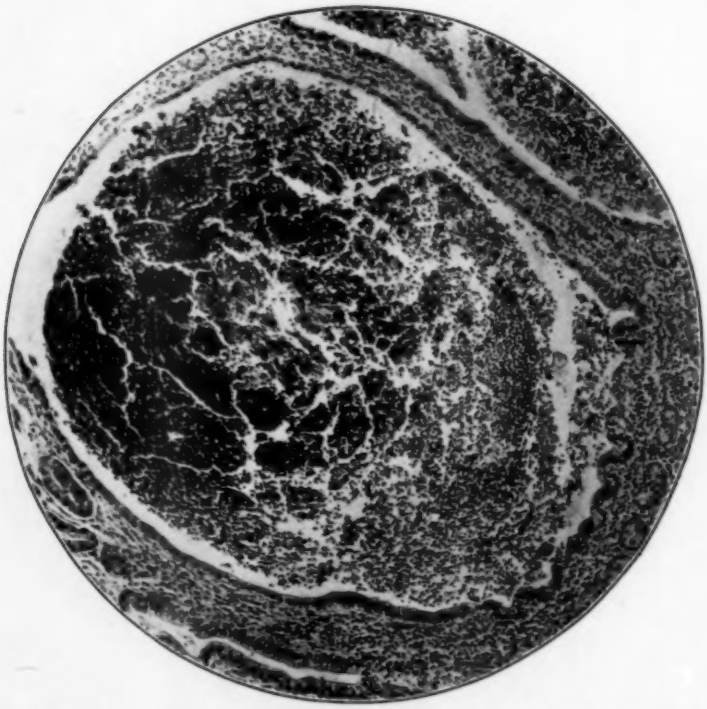


Fig. 3.—Appendix, Rabbit 106, showing a large clump of necrotic material, with leukocytes and red blood cells in the lumen of a gland, with invasion of the mucosa in several places. There are many eosinophils, with a considerable number of leukocytes in the adjacent submucosa.

is a matter difficult of explanation; however, it certainly cannot be attributed to the effect of a varying oxygen tension, to which the organism might have been subjected, as suggested by Rosenow, since it was constantly maintained on plain blood agar slants in cotton-stoppered tubes. This variation in the tendency to attack the appendix at different times is one which should receive the most careful consideration in the interpretation of experiments, since one would be

very prone to error if the organism was not studied over a sufficient period.

It was found that the streptococcus still retained its ability to attack the appendixes of some rabbits when inoculations (125, 126 and 127) were made thirty-eight days after the original isolation, hemorrhages occurring in the appendix of Rabbit 127. As appendiceal lesions occurred in five of twelve rabbits injected during the last eight days, as against no appendicitis in six rabbits in the previous sixteen days, it would appear that the animals themselves must possess peculiar tissue variations, thus limiting the precision with which the biologic characters of an organism can be determined by its effect on living animal tissue. This observation is one of first importance. In any event, the result obtained by injecting the twenty-five rabbits of this group with successive generations of a *S. salivarius* from a parent strain derived from the tonsil of a patient in the height of an attack of acute appendicitis, have demonstrated that the invasive quality of this bacterium, a recognized member of the *S. viridans* group commonly found in the mouth, is a most variable quantity. Moreover, we are not inclined to believe that these peculiarities can be attributed to special methods, as we have at no time followed technic other than that described, which in itself is but one of the authoritive present-day bacteriologic practices.

Material from the tonsils of four other appendicitis patients cultured in the manner described and injected into ten rabbits, produced lesions in the appendixes of five of these animals. Three of the ten rabbits (56, 61 and 68) received the sediment from the entire growth, Rabbits 56 and 61 showing their appendixes involved. A streptococcus (*S. mitis*) was isolated from the original material in but one instance, and the rabbit (68) receiving this mixture showed no change in its appendix. However, a streptococcus pyogenes vulgaris was recovered from the appendix of Rabbit 61, and when inoculated in full amount into the ear vein of Rabbit 74, the animal's appendix was unchanged. As there were no other lesions found in this animal's body, it is probable that the culture was sterile. The animal died four days later with the cultures at necropsy negative (heart blood, bile, knee joint). Thus with a total of thirty-five rabbits injected with organisms obtained from the tonsils of appendix patients, sixteen developed lesions in their appendixes. Four of the above sixteen were inoculated locally into the appendix artery, and in one case into the lumen of the organ, so that there were but eleven animals treated intravenously which exhibited appendicitis. It was worthy of note, however, that where the organisms were given into the appendiceal artery there was little tendency toward localization exclusively in the appendix tissues. Even in such an experiment where the organisms were afforded every opportunity of

localizing only in the appendix, it was found that they filtered through the tissues of this organ, and once having gained entrance to the general circulation, the picture of acute bacteremia was developed.

MATERIAL FROM APPENDIXES (TABLE 3)

The appendixes from which material was used have been divided into groups comprising normal organs, acute ulcerative, acute gangrenous and chronic appendicitis. Ten rabbits were inoculated with the material obtained from two normal appendixes, only three of which developed lesions in their appendixes. One animal (36) injected with a mixture of *Streptococcus mitis, B. coli-communis* and an influenza-

TABLE 3.—RESULTS OF INOCULATIONS—

Case	Source	Organisms	Rabbit No.	Rabbits Injected	Appendix	Stomach	Skin	Lung
9	Normal appendix....	S. mitis; B. coli-communis; Influenza-like B.	36	1	...	1	...	...
49	Acute ulcerative appendicitis	S. fecalis.....	39, 73	2	...	2	...	1
		S. fecalis; B. coli-communior; Staph. albus	41	1				
67	Chronic appendicitis	B. acidi-lactici; Staph. albus	55	1	1	1	1	1
		B. acidi-lactici.....	63, 93, 94	3	2	3	3	3
		Staph. albus.....	65	1	...	1	...	...
		Pneumococcus (R 55).....	89	1	...	1	...	1
69	Acute gangrenous appendicitis	B. acidi-lactici.....	60, 66, 76	3	2	2	3	2
		B. acidi-lactici (R. 76).....	86	1	1	1	...	1
		Staph. albus (R. 73 and 76)	87	1	1	...	...	...
70	Acute ulcerative appendicitis	B. coli-communior.....	62	1	...	1	1	1
72	Chronic appendicitis	B. coli-communis; B. xerosis	67	1	1	1	1	1
74	Chronic appendicitis	B. coli-communis.....	69	1	...	1	...	...
75	Acute gangrenous appendicitis (perforation)	B. acidi-lactici.....	70	1	1	1	1	1
76	Pelvic fluid (Case 75)	Staph. albus; B. Friedlander; B. xerosis	71	1	1	1	1	...
78	Acute gangrenous appendicitis	B. acidi-lactici.....	72	1	1	1	1	1
82	Normal appendix....	B. coli-communis.....	101, 102, 103	3	1	3	3	3
		S. equinus (R. 101).....	110, 111, 112, 116, 117, 118	6	2	4	4	5
83	Abscess, abdominal incision (Case 69)	S. subacidus.....	81, 106, 107, 108, 113, 114	6	...	3	4	1
	12 cases in all.....	.....	.....	36	14	28	23	22

like organism from one of these appendixes exhibited no change in its appendix, while three rabbits (101, 102 and 103) which received a *B. coli-communis* isolated from another normal appendix, showed one (103) with its appendix affected. A *S. equinus* recovered from the gallbladder of Rabbit 101 was subsequently inoculated into six rabbits (110, 111, 112, 116, 117, 118), two of which animals had their appendixes affected.

—WITH MATERIAL FROM APPENDIXES

Heart	Duodenum	Small Intestine	Joint	Thymus	Cecum	Eye	Pericardium	Pleura	Gallbladder	Muscle	Large Bowel	Periarticular	Liver	Endocarditis	Kidney
1	...	...	...	...	...	...	...	...	...	...	...	...	...	1	
1	2	...	...	1	...	1	1	...	...	...	...	...	1		
1	1	1	1	...	1	1	...	...	...	...	1	...	1	...	1
2	1	2	2	...	2	1	...	...	...	1	1				
...	...	...	...	...	...	...	...	...	1						
1	...	...	...	1	...	...	...	...	...	...	...	1			
2	3	3	2	2	...	1	1	1	3	2	1				
1	...	1	1	1	...	...	...	...	1						
...	1	1	...	...	1										
1	1	1	1	1	1	1	...	...	...	...	...	1	...	1	
1	1	1	1	1	1	1	1	1	...	1	...	...	...	1	1
1	1	1	1	...	1	1	...	...	1						
1	1	1	...	...	1	1	...	...	...	...	1				
1	1	1	1	1	...	1	...	...	...	...	1	...	1	...	1
2	2	1	3	3	...	1	3	3	1	...	...	...	1		
2	3	...	...	1	2	...	...	1	...	2	...	1			
2	1	1	...	...	...	...	1	1	...	...	...	1			
21	19	15	13	12	10	10	7	7	7	6	5	4	4	3	3

Of the animals injected with material from cases of acute ulcerative appendicitis, none had the appendix involved. Three animals (39, 41 and 73) received cultures of organisms isolated from one case. The first, 41, was given the mixture of isolated organisms including *S.*

fecalis, B. coli communis and *Staphylococcus albus,* while 39 and 73 received pure cultures of *S. fecalis.* The appendixes of all of these animals were unaffected. Likewise another rabbit (62), inoculated with a *B. coli-communis* from a second case of acute ulcerative appendicitis, escaped with its appendix unchanged.

Three cases of acute gangrenous appendicitis yielded pure cultures of *B. acidi-lactici.* Three animals (60, 66 and 76) injected with the material from one case presented two diseased appendixes (60, 66).

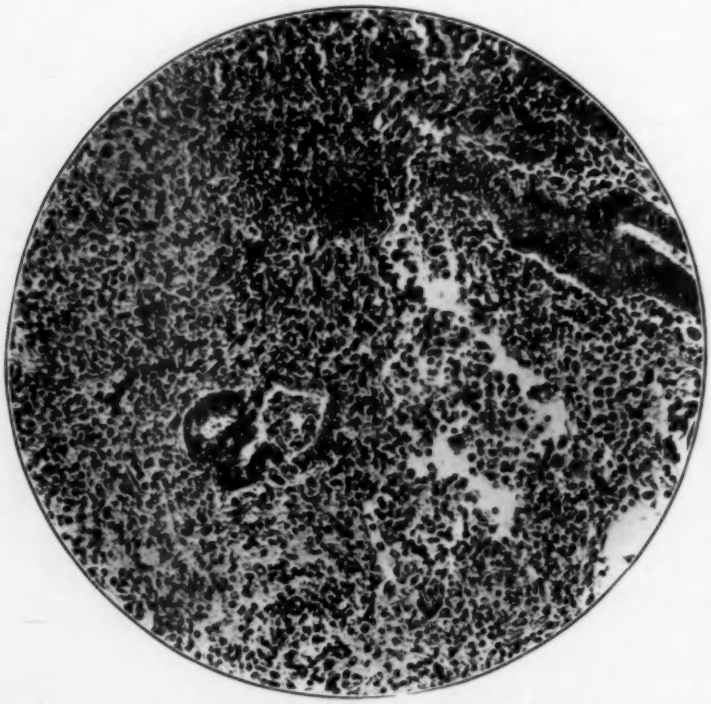


Fig. 4.—Appendix, Rabbit 80, showing an infiltration of leukocytes, lymphocytes and endothelial cells in the submucosa. A clump of débris with leukocytes is observed in the lumen of the gland.

Two other animals (70 and 72) inoculated, respectively, with the material from the other two cases, showed alterations in the appendix. A rabbit injected with the mixed culture (76)—(*B. Friedländer, Staphylococcus albus, B. xerosis*)—from the pelvic fluid from Case 75, had an affected appendix at necropsy. Six animals inoculated with a *S. ignavus* (83), obtained from the infected wound of Case 69 showed no alteration in their appendixes. Another animal treated with a

B. acidi-lactici (Blood 76) into the appendix artery, showed a well-marked appendix lesion, together with involvement of other organs. A second animal (87) received a mixed *Staphylococcus albus* (73 and 76) into the appendix artery, and in addition to the appendix, the duodenum, the small intestine and the cecum were involved.

Of eight rabbits (55, 63, 93, 94, 65, 89, 67 and 69) which received material from cases of chronic appendicitis, four (55, 63, 93 and 67)

Fig. 5.—Appendix, Rabbit 59, showing necrosis of germinal center of a follicle with infiltration of leukocytes and lymphocytes.

were noted to have changes in the appendix. In the first case (B 67) one rabbit (55) was given a mixed culture of *B. acidi-lactici* and *Staphylococcus albus* and at necropsy the appendix was found affected. Subsequently, three other rabbits (63, 93 and 94) were treated with pure cultures of the *B. acidi-lactici* and two (63 and 93) developed appendiceal lesions. One rabbit (65), injected with a pure culture of the *Staphylococcus albus,* exhibited no change in its appendix. A pneumococcus recovered from the blood of rabbit 55 disclosed an unaltered appendix in rabbit 89 when this animal received a full dose

of the organism intravenously. In the second case (B 72) Rabbit 67 was inoculated with a mixture from which *B. coli-communis* and *B. xerosis* were recovered, with the result that its appendix was involved. Another rabbit (69) injected with a culture of *B. coli-communis* from a third case (B 74) of chronic appendicitis, escaped with its appendix unchanged.

The tabulated results appear in Table 2 and show the type of case, the organisms used and the frequency with which the different organs

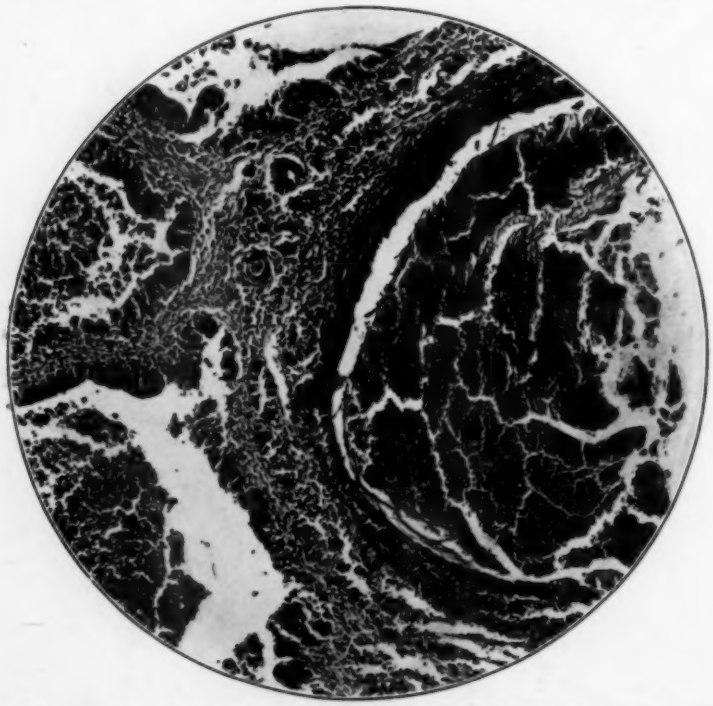


Fig. 6.—Appendix, spontaneously dead Rabbit P-13, showing a clump of necrotic débris, with red blood cells in a widely dilated gland. The lining mucosa has been destroyed and a connective tissue proliferation has taken place.

were attacked in these experiments. Of seven animals injected with the mixed cultures from the original material in Cases 9, 49, 67, 72 and 76, but three developed lesions in the appendixes. Nine animals inoculated with pure cultures of *B. acidi lactici* gave seven affected appendixes, while two mixed cultures containing *B. acidi lactici* and *B. Friedländer*, respectively, produced an appendix lesion in two rabbits. Pure cultures of *B. coli-communis* from two cases gave appendicitis in one

of four animals as against two mixed cultures containing this organism which showed an appendix in but one of two rabbits. One rabbit inoculated with a pure culture of *B. coli-communior,* and three receiving doses of a mixed culture containing this organism, developed no changes in the appendixes. Two separate cultures of *Staphylococcus albus* when given, respectively, to two rabbits resulted in the appendix being involved in but one, which was the result of a local experiment. In five animals that received doses, respectively, of three different mixed cultures containing *Staphylococcus albus,* but two had an altered appendix. These latter two animals had received material which also contained in one case a *B. acidi-lactici* and in the other a *B. Friedländer.* With the green streptococci from appendixes, two of the six animals injected with a pure culture of *Streptococcus equinus* gave an affected appendix, while all of four which received doses of two mixed cultures containing in the one *S. mitis* and in the other *S. fecalis,* were negative for the appendix. Six animals injected with cultures of a hemolytic streptococcus (*S. subacidus*) gave no appendixes. The use of the appendix material has afforded several varieties of organisms, and rabbits injected with such an array of bacteria showed the appendixes affected in our experiments in the ratio of 14 to 36, about 40 per cent. Again, where the rabbits were treated with cultures from the tonsils of appendix patients, containing mostly pure green streptococci, the appendix was involved in the ratio of 16 to 35, about 46 per cent.

MATERIAL FROM NONAPPENDIX CASES (TABLE 4)

A third group of fifty animals comprising those inoculated with organisms from the tonsils and adenoids of persons not affected with appendicitis, showed thirty of them with appendix lesions. Thirteen of these animals were treated with cultures made from the tonsils of fracture patients who were otherwise in good health, with the result that five exhibited altered appendixes. From seven of these tonsils a *S. viridans* was recovered. The *S. salivarius* six times associated with a *S. equinus* in one case and in the remaining tonsil a *S. mitis.* Of the seven animals injected, respectively, with the separate cultures, but two showed appendicitis, one with a *S. salivarius* and the other with the *S. mitis.* Another of the tonsils yielded a *S. anginosus.* One animal treated with the original material developed appendicitis. Subsequently pure cultures of this organism were injected into two animals, one of which only showed an altered appendix. The cultures from the remaining two tonsils gave in one case a *Staphylococcus albus* and *B. xerosis,* while in the other only a *Staphylococcus albus* was found. Two rabbits treated, respectively, with these materials had involved appendixes. The remaining thirty-seven animals of this group were treated with organisms obtained from three cases of chronic tonsillitis

TABLE 4.—Result of Inoculations—

Case	Source	Organisms	Rabbit No.	Rabbits Injected	Appendix	Stomach	Heart	Lung	Joint	Skin
57	Tonsil (Colles fracture)	S. salivarius; S. equinus; Staph. albus	44	1	...	1	1	...	...	1
58	Tonsil (fracture humerus)	S. salivarius; Staph. albus	45	1	1	1	...	1	...	1
59	Tonsil (fracture neck, femur)	S. mitis; Staph. albus	47	1	1	...	...	1	...	1
60	Tonsil (left Pott's frac.)	S. salivarius; Staph. aureus; B. xerosis	48	1	...	...	...	1	...	1
		S. salivarius.....	35	1	...	1	1	1	...	1
61	Tonsil (fracture small finger)	Staph. albus; B. xerosis	49	1	1	...	...	...	...	...
62	Tonsil (fracture ribs)	Staph. albus.....	50	1	1	1	1	...	...	1
63	Tonsil (fracture skull)	S. salivarius.....	51	1	...	1	1	1	...	1
64	Tonsil (Pott's fracture)	S. salivarius.....	52	1	...	...	1	1	...	1
65	Tonsil (fracture femur)	S. anginosus; Staph. albus	53	1	...	1	1	1	...	1
		S. anginosus.....	57, 75	2	1	2	1	2	...	2
66	Tonsil (fracture patella)	S. salivarius.....	54	1	...	1	1	1	...	1
88	Chronic tonsillitis	S. pyogenes-vulgaris; Staph. flavus	134, 135, 136, 137	4	3	3	4	3	4	3
		S. pyogenes vulgaris	150, 151	2	1	2	2	1	1	1
89	Chronic tonsillitis	S. pyogenes-vulgaris; S. salivarius; Staph. aureus	138, 139, 140	3	2	1	2	2	3	1
		S. pyogenes-vulgaris	156, 157, 162, 163	4	2	3	1	2	3	...
		S. salivarius.....	158, 159	2	1	2	...	1	1	...
		S. salivarius; S. pyogenes-vulgaris	164, 165	2	1	2	...	2	1	1
		S. pyogenes-vulgaris (gland, Rabbit 139)	166, 167	2	2	2	1	1	1	...
89	Hypertrophy, adenoid	S. pyogenes-vulgaris; pneumococcus; Staph. aureus	142, 143, 144, 145	4	3	2	4	4	4	2
		S. pyogenes-vulgaris	152, 153	2	2	2	1	1	2	1
		S. pyogenes-vulgaris; pneumococcus	154. 155	2	2	2	2	...	...	...
		S. pyogenes-vulgaris (gland, Rabbit 144)	168, 169	2	2	2	1	...	2	1
		S. pyogenes-vulgaris (knee, Rabbit 145)	170, 171	2	...	2	2	1	1	...
90	Chronic tonsillitis	S. infrequens; B. Friedlander; Staph. aureus	146, 147, 148, 149	4	3	3	4	4	2	2
		S. infrequens (gland, Rabbit 146)	172, 173	2	1	1	1	1	...	1
	14 cases studied	.....	.....	50	30	38	33	33	25	25
91	Infected hand...	S. pyogenes-vulgaris; Staph. albus	174, 175, 176, 177	4	2	3	2	4	...	...
	15 cases in all..	.....	.....	54	32	41	35	37	25	25

—WITH MATERIAL FROM NONAPPENDIX CASES

Duodenum	Thymus	Muscle	Small Intestine	Brain	Cecum	Large Bowel	Pleura	Pericardium	Endocarditis	Periarticular	Eye	Kidney	Liver	Adrenal	Cord	Gall Bladder
...	...	...	...	...	...	...	...	...	1							
...	1	1														
1	...	...	...	...	...	...	...	...	1	...	1					
...	...	...	..	...	...	...	...	...	1							
...	...	..	...	...	...	...	1	...	...	...	..	1	1			
...	...	...	..	...	...	...	1	...	1							
1	...	1	..	...	...	...	...	..	1							
...	...	1	...	...	...	...	1	...	1	...	1					
1	...	1	...	...	...	...	1									
...	1	1	...	...	...	...	...	...	...	...	..	...	1			
1	1	...	1	...	1	...	1	1	...	1	1					
1	...	1	...	...	...	...	...	1								
3	2	3	2	1	2	1	2	2	...	1	1	1				
...	...	1	...	1												
2	2	1	2	2	2	2	1	2	..	1						
2	3	1	1	...	...	...	...	1	1	...	..	...	....	....	1	
2	1	...	1	...	1											
...	1	1	1	1	...	...	...	...	...	1						
1	...	1	1	2												
4	3	3	3	1	3	3	...	...	..	1						
...	1	...	...	2												
...	1	...	...	1												
1	...	1	1	2	...	...	...	...	...	...	..	...	....	2		
...	1	...	...	2	...	...	...	1								
2	3	1	4	1	2	2	...	..	1	1	..	1	....	....	....	1
1	...	1														
23	21	20	17	16	11	8	8	8	8	6	4	3	2	2	1	1
...	2	...	...	...	...	1	1	...	...	...	..	...	2			
23	23	20	17	16	11	9	9	8	8	6	4	3	4	2	1	1

and a mass of adenoid tissue from one of the patients. Here the predominant organism was a *S. pyogenes vulgaris*, and it was found that the material from these cases gave a higher number of animals with affected appendixes. Of sixteen rabbits inoculated with pure cultures of a hemolytic streptococcus, ten gave positive evidence of reaction in the appendixes. Fourteen of these animals were given doses of *S. pyogenes-vulgaris* with the result that nine developed appendicitis.

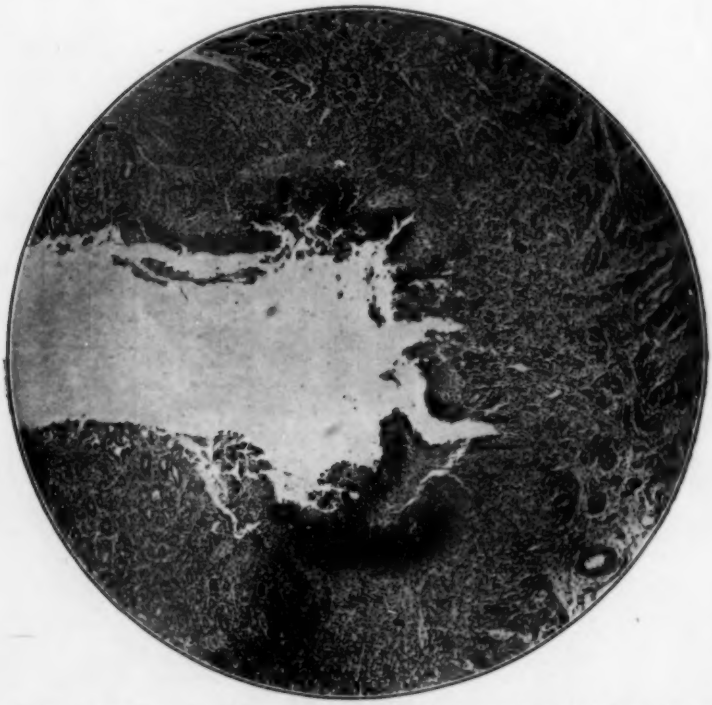


Fig. 7.—Stomach, Rabbit 69, which animal died immediately following injection, showing an ulceration in the pyloric ring, with necrosis of the mucosa and underlying tissues. Many eosinophils are scattered throughout the submucosa.

The two remaining rabbits received cultures of *S. infrequens* isolated from a gland about the base of the appendix in Rabbit 146, and one of these had its appendix involved. Four other rabbits inoculated with separate cultures of *S. pyogenes-vulgaris*, recovered from glands about the appendix of two rabbits (139 and 144), revealed changes in their appendixes. In three cases (188, 189, 190) the original material contained only one type of streptococcus, and of twelve rabbits treated

with these particular mixtures, nine had evidence of alteration in the appendixes. One of the mixtures, however, also contained a pneumococcus in addition to a *S. pyogenes-vulgaris,* and here three of four animals showed an appendicitis. This condition also occurred in the same ratio in each of two other groups of four rabbits injected, respectively, with mixtures containing in one a *S. pyogenes-vulgaris,* and in the other a *S. infrequens.* Two rabbits inoculated with a mixture of

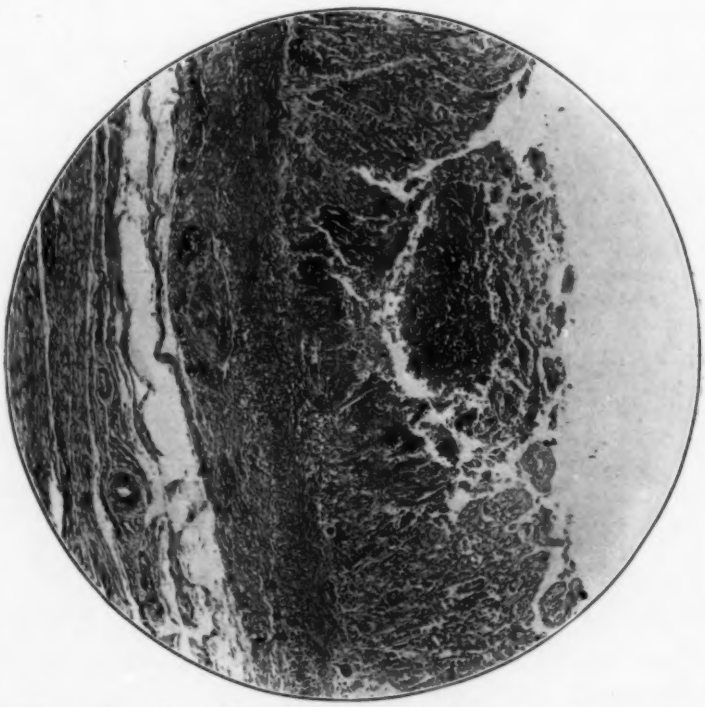


Fig. 8.—Stomach of Rabbit 135, showing ulceration and necrosis of mucosa, with hemorrhage and leukocytes scattered throughout the necrotic material. The infiltration of leukocytes extends to the outer border of the submucosa, but not beyond it.

pure cultures of the pneumococcus and *S. pyogenes-vulgaris* from Case 89 (adenoid), exhibited appendix lesions. The material from one case (89, tonsil) included both a *S. pyogenes-vulgaris* and a *S. salivarius,* and of three animals which received this mixture, two gave positive evidence of appendix affection. One of two animals injected with a pure culture of the *S. salivarius* had appendicitis, while four of six animals which received the pure *S. pyogenes-vulgaris* had

appendicitis. This is interesting in view of the fact that but one of two rabbits inoculated with a mixture of the pure isolated organisms showed an appendicitis. Of the fifty rabbits used in this group of non-appendix tonsils, forty-eight received material containing streptococci. Twenty-eight of these animals had affected appendixes. The material injected into the remaining two animals did not contain streptococci. The appendixes of both animals, however, showed hemorrhages. Thus thirty of the fifty rabbits had involved appendixes, making exactly 60 per cent.

In addition to the above group, four rabbits were inoculated with divided doses of a culture of pus from an infected hand. A *S. pyogenes-vulgaris* and *Staphylococcus albus* were recovered from the mixture. Two of the four animals showed hemorrhages in the appendix.

GENERAL RESULTS

A general review of the entire group of 125 animals demonstrated that the rabbits injected with hemolytic streptococci, or material including these organisms, showed a higher number of affected appendixes than those animals inoculated with green streptococci. Fifty-five animals received cultures containing hemolytic streptococci, thirty of which had an appendix lesion. Of this number there were with *S. pyogenes-vulgaris*, 23 of 36, with *S. infrequens* 4 of 6, with *S. anginosus* 1 of 3, and with *S. subacidus* 2 of 10. Forty-six rabbits were treated with material containing green streptococci, sixteen of which had appendicitis. These were divided in the following way: 13 of 34 with *S. salivarius*, 1 of 3 with *S. mitis*, 2 of 6 with *S. equinus*, while there were none of 3 with *S. fecalis*. Not only was it found that rabbits treated with hemolytic streptococci more often showed appendicitis, but that these animals also developed a more severe type of bacteremia, affecting the different organs of the body more frequently. It is therefore of the utmost importance in dealing with streptococci that the lesions produced by them should be considered in terms of the individual type of streptococcus.

Fifteen rabbits were treated with material including organisms of the capsulated gram-negative group of bacilli, and 12 were found to have appendicitis. Of this number 9, inoculated with pure cultures of *B. acidi-lactici*, gave 7 with appendicitis, while 1 rabbit treated with a mixture of *B. acidi-lactici* and *Staphylococcus albus* also had appendicitis. Four rabbits treated with a mixed culture of *S. infrequens*, *B. Friedländer* and *Staphylococcus aureus* showed 3 with appendicitis, while one rabbit treated with a mixture of *B. Friedländer*, *Staphylococcus albus* and *B. xerosis* had an affected appendix. Of the rabbits injected with material containing *B. Coli*, but 2 had appendicitis. These consisted of 1 of 4 animals inoculated with pure cultures of *B. coli-*

communis, 1 of 2 with mixed cultures including this organism, while all of 4 treated with material containing *B. coli-communior* were negative.

Five of six animals injected with cultures from which staphylococcus was isolated as the principal organism, revealed appendicitis at necropsy. One of these animals was injected locally into the appendiceal artery. However, the cultures at necropsy in four of the animals

Fig. 9.—Duodenum, Rabbit 117, showing extensive hemorrhage into the mucosa and about the glands in the submucosa.

showed additional organisms to those isolated from the original culture. In two cases a *B. acidi-lactici* was isolated, once from bile and once from peritoneum, while in another, *B. coli-communior* was recovered from a gland at the base of the appendix. In the fourth rabbit a *S. pyogenes-vulgaris* was found in the appendix.

A pure culture of pneumococcus produced no appendicitis in one rabbit, while mixtures of pneumococcus and *S. pyogenes-vulgaris* given to six animals showed an appendix lesion in five.

These experiments have demonstrated that the rabbit's appendix is prone to exhibit alterations in structure when organisms are administered intravenously into the blood stream. Although it was found that certain organisms were more frequently associated with such lesions than others, there was no appreciable difference in the anatomic structure of the lesions except one of degree. Of the coccaceae, the hemolytic streptococci produced appendicitis most frequently, while among the bacilli the gram-negative capsulated bacilli gave the most constant results. It may also be said of these latter organisms that they gave a larger percentage of positive results than any of the other bacteria used. The general consideration of the entire number of 125 animals shows that sixty-two, treated with a variety of organisms including both hemolytic and nonhemolytic streptococci, pneumococci, staphylococci, *B. mucosus-capsulatus* and *B. coli*, had appendicitis.

The lesions observed in the appendix consisted for the most part of bright colored hemorrhages varying in size from clustered pinpoint dots to irregular small patches 2 to 3 mm. in diameter. These areas did not tend to follow any regular distribution in the tissues of the organ, as they were at times visible from either the mucosa or serosa, while again they could not be easily seen unless the wall of the organ was sectioned. In general, however, it may be stated that the hemorrhagic foci were developed principally in the region of the deeper tissues of the wall, as in many cases small hemorrhages were observed in this region when other areas were free. Where the mucosa was chiefly affected there was found in a large number of cases a diffuse speckling of the lining, with irregularly sized hemorrhages, many of which formed small confluent patches. Over the larger areas the mucous covering was very apt to be somewhat roughened. In some appendixes the mucosa had a slightly moth-eaten appearance.

MICROSCOPIC APPEARANCES

Microscopically, the hemorrhages observed in the appendixes consisted of varying degrees of red-cell infiltration into the tissues of the organ beneath the mucosal lining. For the most part this reaction was present about the follicles in the submucosa, although hemorrhage quite often occurred within the follicles themselves. The hemorrhages about the follicles were found in the interstitial tissue between these structures, frequently outlining a follicle, and separating the component parts of the surrounding connective tissue. Frequently the hemorrhage was noted breaking through the connective tissue sheath of a follicle when it replaced the lymphoid cells in the immediate neighborhood. At times the red cell infiltration was quite diffuse and extended inward close to the mucosal layer. In the majority of such areas, the amount of inflammatory cell reaction was a negligible quan-

tity. That is, in the areas where the hemorrhagic infiltration was marked, inflammatory cells were usually absent. In the areas where the hemorrhage was less in amount, or absent, however, the interstitial tissue showed scattered polymorphonuclear leukocytes. In some places these cells were aggregated into fairly compact masses, with evidence of necrosis, accompanied by nuclear debris. Eosinophils were present in large numbers in the submucosal tissue of many appendixes. These

Fig. 10.—Liver, Rabbit 133, showing infiltration of leukocytes and scattered areas of necrosis about a central vein.

cells were mostly observed in the tissues about the bottom of the crypts and in the interstitial tissue between the ducts. Phagocytic endothelial cells, and at times multinucleated phagocytes, were noted in the areas of inflammatory reaction. The germinal centers of the follicles commonly exhibited proliferation of the cells. This was more readily observed where the hemorrhage was not so marked. These areas often showed slight amounts of hemorrhage with infiltration of polymorphonuclear leukocytes attended by necrosis of the proliferating cells and

scattered nuclear debris. The mucosal lining and glands were without change in all of these specimens. A number of appendixes which showed no evidence of alteration in the gross, as could be determined by hemorrhage, gave interesting microscopic pictures. The mucosal lining and gland structures were intact. In the submucosal tissue there was scattered polymorphonuclear leukocytic infiltration. At times the cells formed patchy areas with the leukocytes plugging small lymph channels. In other areas the infiltration was more diffuse, with a hyalin-like character to the involved tissue. There were clumps of debris containing leukocytes in the lumina of some glands. The lining cells of these structures were undisturbed. Again, in other sections, small areas of the mucosa were absent, with tiny capillaries and developing fibroblasts in the underlying tissue. The bases of the crypts were present with the overlying tissue loose and edematous. There was no exudate on the surface. Again, sections were observed in which the lumina of the glands were dilated by large clumps of necrotic material through which leukocytes were scattered. Most of these gland structures showed intact epithelial lining cells; however, in some places the lining cells were absent with extension of the inflammatory cells for a short distance into the submucosal tissue. Here the reaction was limited and did not have the character of acute inflammation. The prominent feature in the submucosa of these sections was the presence of many eosinophils. The follicles in the submucosa were not involved. In the most marked specimen of this type coccidia were found lying in the lumina of some of the glands, with the loss of the lining cells of the gland and the presence of many eosinophils and some leukocytes in the surrounding tissue. The same type of reaction, with the presence of coccidia, was noted in several appendixes which exhibited hemorrhages in the gross. A similar reaction was noted in the appendixes of two spontaneously dead rabbits (Fig. 6).

Six rabbits injected with sterile cultures showed interesting changes in the appendixes. These animals are not included in the series of 125 rabbits, as the appendixes exhibited no evidence of alteration in the gross. Sections of the organs showed marked proliferation of the germinal centers of the follicles. In some of these areas there was an invasion of leukocytes with necrosis of the proliferating cells. Large phagocytic endothelial cells were frequently observed in these reactions. The leukocytic infiltration occasionally broke through the capsule of the involved follicles, with the exudate coming to involve the surrounding interstitial tissue. The lymph spaces often were plugged with inflammatory cells in the region of such areas. The leukocytic infiltration extended to the submucosal tissue where there were also many eosinophils and at times small collections made up of both types of these cells. The component parts of the mucosa were free from any

sign of injury. In several places, however, leukocytes were found passing through the epithelial covering. In such places the epithelial cells were unaltered and appeared to be separated by the migrating leukocytes.

Where the injections were made into the appendiceal artery without any important interference with the blood supply, scattered areas of hemorrhage were found in the tissues of the organ. The follicles

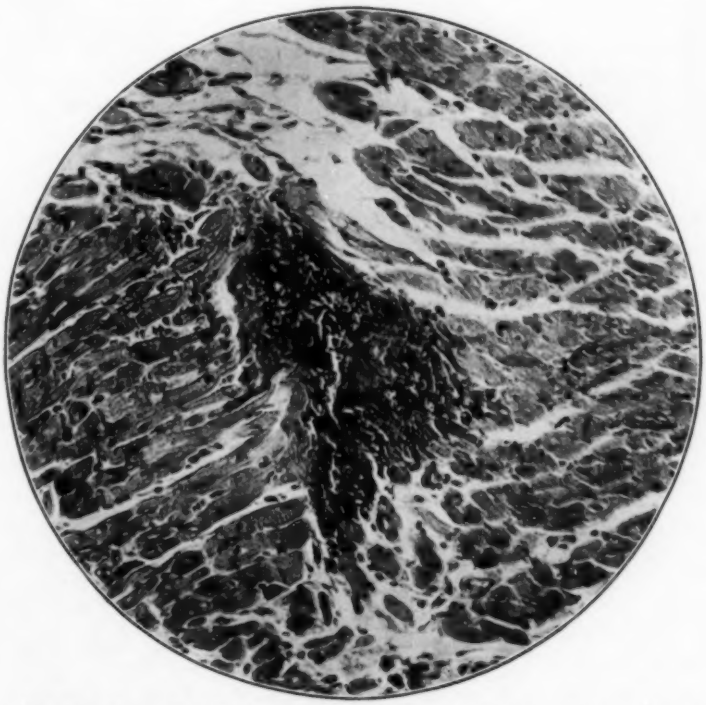


Fig. 11.—Heart, Rabbit 120, showing an area of infiltration about a clump of cocci. The infiltration consists mostly of lymphocytes, with some large mononuclears and a few leukocytes.

were almost replaced by hemorrhage, only narrow rings of surrounding lymphocytes remained. In most of the follicles hemorrhage formed the prominent feature, although in some, scattered leukocytes were observed. Large phagocytic endothelial cells were present in some of the follicles. The mucosa overlying these areas was occasionally absent. However, there was no acute exudate on the surface.

Where the blood supply of the appendix was altered at the time of

inoculation into the appendiceal artery, the organ showed marked alteration. There was an exudate on the serosa, with necrosis of the different layers of the wall and invasion of leukocytes.

The study of the rabbits' appendixes showed that where hemorrhage was the prominent feature, inflammatory cell infiltration was not marked. Proliferation of the germinal centers of the follicles with leukocytic infiltration and necrosis occurred in appendixes in which there was no evidence of hemorrhage, although the two conditions frequently occurred together. In other appendixes the submucosal tissues presented leukocytic and eosinophil cell infiltration while the follicles and mucosa were free from change. Large clumps of necrotic material were found in the ducts at times, with only occasional small areas of the lining cells absent. Coccidia were found in some appendixes with disturbance of the mucosa of the duct, and a surrounding infiltration of eosinophils and leukocytes. Sections stained by Gram's method frequently showed clumps of organisms in small capillaries, which, as a rule, were unattended by surrounding inflammation. Where the organisms were injected directly into the appendiceal artery, massive hemorrhage took place into the follicles and surrounding tissue, with some involvement of the mucosa. The presence of coccidia in some appendixes, and the fact that the reaction in the submucosa commonly did not have the typical picture of acute inflammation, would tend to show that some of the changes observed existed previous to the inoculation. In this connection the relation of *Oxyuria vermicularis* to human appendicitis may serve to explain how coccidia would act as an irritant to favor the production of appendicitis in rabbits. Only the appendixes which exhibited hemorrhages in the gross were counted. The number would be considerably more than sixty-two if those showing microscopic changes were also included. Lesions similar to those which we have observed were found in the appendixes of normal rabbits so frequently by Ghon and Namba[6] that they were loath to place much importance on the changes which occurred in rabbits' appendixes after the intravenous injection of streptococci, staphylococci and pneumococci. The hemorrhages which formed the prominent feature in the appendixes listed as having changes were essentially an intramural condition and were present in the majority of instances without evidence of mucosal injury. From the reactions which were noted in the other organs there is no doubt that the inflammatory infiltration in the tissues of the appendix at times depended for its origin on the organisms injected. The character of the lesions in many appendixes, however, and the presence of coccidia suggest that quite frequently a previ-

6. Ghon and Namba: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1912, **52**, 130.

ously existing inflammatory reaction may have been present in the organ.

The appendix of the rabbits was not the only organ affected. Hemorrhages in the stomach, lungs, skin, and endocardium were noted more frequently than they were in the appendix. The entire gastrointestinal tract was commonly the seat of hemorrhages and presented this picture in the following order: stomach, appendix, duodenum,

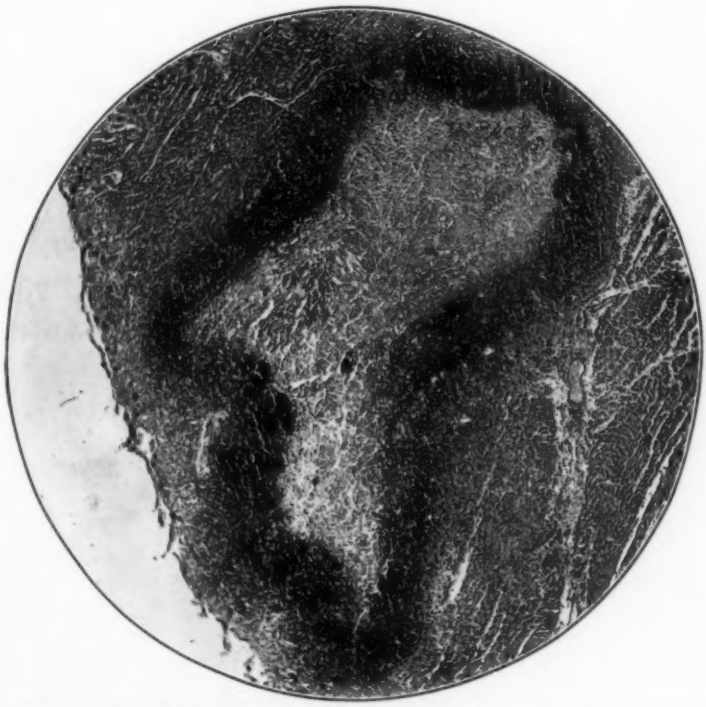


Fig. 12.—Heart, Rabbit 53, showing an infarcted area, with the inflammatory zone consisting mainly of lymphocytes.

small intestine, cecum and large bowel. Hemorrhages were also noted in the thymus, muscle, pericardium, pleurae, periarticular tissues and eye, in the order named. Almost without exception the spleen was enlarged, with tense capsule and soft deep-colored pulp. Vegetative endocarditis was found in fourteen rabbits. Where there was no hemorrhage, acute lesions were found at times in the myocardium, liver, kidney and skeletal muscles. Sometimes these areas could be recognized in the gross as small, yellowish foci. The joint fluid of the knees

was frequently cloudy, or the synovial lining quite pink, and organisms were recovered from these in forty-eight rabbits. Cultures made from the brain in forty-six cases gave twenty-one positive results. A large number of these animals showed small petechiae in the lining of the lateral ventricles, and five of the animals showed small hemorrhages in the white matter of the cord. Ten positive cultures were obtained from the gallbladder. We wish to reserve the detailed description of these changes for a separate communication. The summary (Table 5) indicates the relative frequency with which the organs were attacked in the different experiments.

The question of the experimental production of appendicitis has occupied the attention of many investigators over a long period of time. In 1885 Ribbert,[7] wishing to study the effect of pathogenic micro-organisms on the appendixes of rabbits, injected *Staphylococcus pyogenes-aureus* through the tip of the organ into the lumen after placing a ligature about its base. Five and one-half hours following this experiment the animal died. The appendix was found filled with

TABLE 5.—

	Rabbits Injected	Appendix	Stomach	Lung	Skin	Heart	Duodenum	Joint
Tonsils of appendix patients	35	16	16	16	21	12	11	10
Material from appendixes	36	14	28	22	23	21	19	13
Material from nonappendix cases	54	32	41	37	25	35	23	25
Totals	125	62	85	75	69	68	53	48

Explanation: Heart = hemorrhage into endocardium. Endocarditis = vegetation visible in the gross.

fluid in which large clumps of cocci were seen, and the mucosa and inner half of the follicles showed many invading organisms, while the remaining coats were free. In the same communication Ribbert claimed that he was able to demonstrate bacteria of all kinds beneath the mucous membrane of the appendix and lower ileum of normal rabbits. In this contention he was substantiated by Bizzozero[8] and more recently by Ghon and Namba.[6] Later Ribbert,[7] in a description of the normal and pathologic anatomy of the human appendix, called attention to the anatomic similarity between the tonsil and appendix. He said the appendix formed a blind sac, and, like the tonsil, communicated with the normally infected body cavities. Further, that just as bacteria can be forced into crypts of the tonsil during swallowing, so a like mechanical condition prevails in the appendix when the cecum is filled with feces. Stöhr[9] has also commented on the same points, particularly in connection with the tonsil. Roux[10] endeavored to produce appendicitis in an artificially made appendix in pigs by introducing foreign bodies. Finding in only one case a perforation between the appendix

7. Ribbert: Deutsch. med. Wchnschr., 1885, **13,** 197; Virchows Arch. f. path. Anat., 1893, **132,** 66.
8. Bizzozero: Centralbl. f. d. med. Wissensch., 1885, **45,** 801.
9. Stöhr: Cor.-Bl. f. schweiz. Aerzte, 1890, **20,** 537.
10. Roux: Congr. française de Chir., 1894, **8,** 213.

and large bowel, he concluded that a foreign body was not sufficient of itself to set up an inflammation.

About this time Lewis[11] directed attention to the apparent relationship between angina tonsillaris and appendicitis, while a little later Robinson[12] pointed out the fact that at times after the beginning of an acute rheumatic attack suddenly an acute typhilitis occurred, or on the other side following this acute appendicitis there was swelling of the joints of a rheumatic nature. That there appeared to be a recognized relationship between tonsillar infection, appendicitis and rheumatism at this time was evidenced by the fact that Jalaguier,[13] Brazil[14] and Sutherland[15] reported similar clinical observations. Jalaguier[13] thought appendicitis was a general infection, as he had noted acute articular rheumatism followed by perityphilitis, and had observed cases of the latter in the course of measles, mumps, typhus, varicella and scarlatina. Brazil[14] had observed two cases of appendicitis complicated with polyarthritis, while Sutherland[15] attempted to explain the coincidence of appendicitis and rheumatism by the presence of rich lymphoid tissue in the appendix, and commented further that just as the tonsil can be the starting place of an acute rheumatism, so also can the appendix be, or vice versa; an appendicitis can arise from a joint which has in turn had its infection from the tonsil. Sahli,[16] viewing the appendix in the light of its anatomic similarity to the tonsil, called attention to its rich supply of lymphoid

—SUMMARY

Thymus	Small Intestine	Muscle	Cecum	Brain	Pleura	Pericardium	Large Bowel	Endocarditis	Periarticular	Eye	Kidney	Liver	Gallbladder	Cord	Adrenal
12	6	3	3	5	2	3	1	4	5	1	4	2	2	4	
12	15	6	10	...	7	7	5	3	4	10	3	4	7		
23	17	20	11	16	9	8	9	8	6	4	3	4	1	1	2
47	38	29	24	21	18	18	15	15	15	15	10	10	10	5	2

Muscle = skeletal muscle 14, heart muscle 15.

tissue and the liability of infection of this tissue from the surface of the bowel, and he referred to a simple appendicitis as an angina of the organ. This view was supported by Nothnagel,[17] who said that the appendix, being rich in adenoid tissue, was as peculiarly susceptible to infection as the tonsil. Helferich[18] and Sunalerg[19] called attention to how quickly an infection invades other organs rich in lymphoid tissue, like the tonsil, neighboring tissue, lymph vessels and closely lying lymph glands. Beck[20] has spoken of the appendix as a large blind sac, and of the tonsil as a conglomeration of blind sacs. On account of this anatomic structure and their connection with body cavities rich in bacteria, both are subjected to the same liability of infection.

11. Lewis: Pathology of the Vermiform Appendix, London, 1893, p. 53.
12. Robinson: Med. Rec., New York., 1895, **48,** 373.
13. Jalaguier: Bull. méd., Paris., 1895, **9,** 615.
14. Brazil: Brit. Med. Jour., 1895, **1,** 1142.
15. Sutherland: Lancet, London, 1895, **2,** 457.
16. Sahli: Kongr. f. inn. Med., 1895, **13,** 201.
17. Nothnagel: Spec. Path. u. Therap., 1908, **17,** 628.
18. Helferich: Kongr. f. inn. Med., 1895, **13,** 241.
19. Sunalerg, Adrian: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1901, **7,** 407.
20. Beck: Samml. klin. Vortr., 1898, New Series, **221,** (Chir., **65,** 1101).

Thus it is seen that even in the earliest studies of appendicitis various phases of the disease were recognized with the advancement of evidence supporting both the enterogenous and hematogenous theories. When the experimental production of appendicitis began to occupy the further attention of investigators, we find that the problem was attacked from many sides, with the result that even at present the pathogenesis of the disease is a much mooted question.

De Rouville,[21] who believed appendicitis had its origin from the lumen of the sac, plugged the canal of the appendix with wool, and found that the organ became diseased only as far as it was obstructed, an observation which has since been ably supported by the work of Aschoff,[1] Oberndorfer[22] and others studying human appendixes containing fecal concretions. Josué[23] used a streptobaccillus isolated from a case of spontaneous appendicitis in a rabbit (Charrin[24]) by injecting it intravenously into other rabbits, and found no localization in the appendixes of the animals. By direct injection of *B. coli* into the appendixes of rabbits, Anghel[25] noted an inflammation of the mucosa and a hypertrophy of the follicles in the submucosa when the organ was ligated at its base. Dominici and Letulle[26] produced an appendicitis in a rabbit one hour after the intravenous injection of *B. typhi.* De Klecki,[27] in a series of experiments, demonstrated that the virulence of the colon bacillus for the appendix can be increased under certain conditions, and also that interference with the nutrition of the appendiceal tissues can give purulent appendicitis without regard to the virulence of the organisms. Mühsam[28] used *B. coli, B. pyocyaneus* and staphylococcus locally in the appendix, and although he was able to produce certain lesions following interference with circulation by crushing and tying off the organ, he came to the conclusion that these experiments were of little value in explaining appendicitis as it occurred in humans. Beaussenat[29] concluded from his experiments that appendicitis is due to a blood infection that commonly comes from the intestinal tract, and the most important predisposing factor for appendicitis is an enterocolitis which lowers the resistance of the appendix and renders it more liable to future infection, especially by the blood.

As evidence that an acute intestinal catarrh may play a part in the production of an acute appendicitis, Ribbert,[7] Riedel[30] and Karewski[31] noted that such a catarrh may establish a chronic lesion in the appendix, which remains long after the intestinal condition has subsided, and may serve to favor the occurrence of an acute appendiceal attack. Oberndorfer[22] has also noted that this sequence of events is a very likely happening, while, on the other hand, Aschoff[1] was loath to take this into consideration as a forerunner of acute appendicitis.

Of the early work concerning the hematogenous origin of appendicitis, the most important was that of Adrian.[4] This author, recognizing the apparent clinical relationship between tonsillitis, appendicitis and rheumatism, endeavored

21. De Rouville: Compt. rend. Soc. de biol., 1896, **3,** 868.
22. Oberndorfer: Frankfurt. Ztschr. f. Pathol., 1908, **2,** 356; Ergebn. d. allg. Pathol., 1909, **13,** 527; Dis. Verhandl. d. deutsch. path. Gesellssch., 1910, **14,** 158; Verhandl. d. deutsch. path. Gesellsch., 1910, **14,** 159; Med. Klin., 1911, **7,** 2048.
23. Joseé: Compt. rend. Soc. de biol., 1897, **4,** 280.
24. Charrin: Compt. rend. Soc. de biol., 1897, **4,** 209.
25. Thése de Paris, 1897.
26. Dominici and Letulle: Semaine méd., 1897, **15,** 112.
27. De Klecki: Ann. de l'Inst. Pasteur, 1899, **13,** 480.
28. Mühsam: Deutsch. Ztschr. f. Chir., 1900, **55,** 143.
29. Beaussenat, Adrian: Mitt. a. d. Grenzgeb., 1901, **7,** 428.
30. Riedel: Arch. f. klin. Chir., 1902, **66,** 1.
31. Karewski: München. med. Wchnschr., 1905, **1,** 433.

to produce appendicitis in rabbits by the intravenous injection of various micro-organisms. For this purpose he employed cultures of streptococci, *Pneumococci*, *B. coli communis*, *B. typhi*, *B. tuberculosis* and *B. anthracis*. The result with all the organisms was a similar lesion consisting of inflammation, hemorrhage and necrosis of the appendiceal follicles. He was so impressed with the relative frequency of these changes in the appendix when compared with the mucosa and Peyer's patches in the remainder of the bowel, that he concluded the appendix of rabbits and humans, owing to the rich adenoid tissue, forms a favorable place for the lodgment of bacteria, just as the joint, the serous lined cavities, lymph glands or other organs supplied with a rich lymphatic apparatus. In this con-

Fig. 13.—Rabbit 48, showing a vegetation on mitral valve.

nection we find that Mori[32] injected streptococcus, *Staphylococcus aureus*, *B. proteus* and *B. coli* into the superior mesenteric artery, and observed other parts of the intestine showing lesions similar to those in the appendix. Mori also states that he found spontaneous appendicitis in laboratory animals.

Again, in 1906, Kretz[3] attempted to prove that the small hemorrhages observed in the mucosa of human appendixes are the initial stage of the virulent type of acute appendicitis as it is observed at operation. Kretz maintained that the infection came by way of the blood from the tonsils, which did not need to

32. Mori: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1903, **12,** 639; Deutsch. Ztschr. f. Chir., 1904, **73,** 123.

exhibit a recognizable inflammation clinically. He based this contention entirely on the fact that he found fibrin in the blood and lymph vessels of the tonsil along with lymphocytes and bacteria. In this connection, Meyer,[33] a student of Aschoff, observed the same condition in twelve of thirty-one pairs of tonsils from patients dying of all causes. From this evidence Aschoff was inclined to believe that these alterations were due to postmortem change. Kretz[3] said that streptococci from the tonsil located in the follicles of the appendix near the germinal center, and that he found streptococci there in pure cultures. When these organisms lodge within the capillaries of the germinal centers of the follicles, they multiply and destroy the capillary wall with resultant hemorrhage and destruction of the follicle, the process finally rupturing through the mucous membrane. The process either ends here or goes on to complete disintegration of the follicle with fibrinous exudate and formation of a crater-like ulcer, from which last condition extensive inflammation of the appendix may occur.

Following the statement of Kretz,[3] pointing to a specific infective agent in appendicitis, a storm of dissent arose among the German authors. Aschoff[1] was chief among those who combated the theory of Kretz, and held that the disease started as an enterogenous infection at the bottom of the crypts, where even in the earliest hours (5) following the outset of the symptoms, the epithelium shows a small accumulation of fibrin and leukocytes. Beneath the fibrin clump, and in the neighboring tissue, many polynuclear leukocytes are found with the neighboring lymph vessels taking part in the inflammation. The leukocytic infiltration advances and finally invades the muscularis and subserosa, the extension of the inflammation into the deeper tissues being in the form of a wedge with the apex at the inflamed crypt. In the fibrin overlying the surface, there are in the earliest stages many bacteria, most of which are intracellular in the form of gram-positive bacilli and diplococci. The primary defect is multiple in most cases. Confluence of the individual areas is very common, leading to phlegmonous infiltration of the appendix. Following this, there may be a breaking down of the muscularis, with the development of abscesses in the wall, going on in some cases to perforation and in others to extensive mucosal ulceration, with a possible destruction of the entire organ.

Aschoff was of the opinion that the areas of hemorrhage which occur in appendicitis are traumatic, as they occur in appendixes where there is no evidence of inflammation whatsoever. In this view he was supported by Fränkel.[34] Although Oberndorfer[33] considered most of the hemorrhages observed by Kretz[7] as being of traumatic origin, he nevertheless said that septic embolic disease of lymph follicles is possible, as he found this lesion in the follicles of the intestine, attended by hemorrhage. Albrecht[35] has discussed similar findings to those of Oberndorfer; he, however, considers the hemorrhages as of traumatic origin, as he has observed fresh hemorrhages in all types and stages of appendicitis. Riedel[36] looked on the areas of hemorrhages as a part of a chronic catarrh which brings about injury to the mucosa, permitting the entrance of infecting agents into the finer lymph vessels, with the subsequent development of an acute inflammation in the appendix, similar to the lymphangitis of the skin seen in erysipelas. The severity of the reaction depends on the invading organisms.

That a rapidly developing lymphangitis can develop in the appendix was supported by Heile,[36] who noted that the rich lymphoid structure of the appendix favors an invasion from a primary epithelial defect, as in the very first hours of an attack there is an exudate on the peritoneum consisting of leukocytes,

---

33. Meyer and Aschoff: Verhandl. d. deutsch. path. Gesellsch., 1907, **11,** 313.

34. Fränkel: Dis. Verhandl. d. deutsch. path. Gesellsch., 1904, **8,** 246. Oberndorfer: Med. Klin., 1911, **7,** 2048.

35. Albrecht: Dis. Verhandl. d. deutsch. path. Gesellsch., 1907, **11,** 318; ibid., 1910, **14,** 158. Wien. klin. Wchnschr., 1909, **22,** 1359.

36. Heile: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1911, **22,** 58; ibid., 1913. **26,** 345.

fibrin and bacteria. Heile further goes on to say that as a streptococcus can be caught in the deep tissues of the follicular tissue of the tonsil and set up an inflammation, the same occurrence is also noted in the appendix. Nowicki[37] believes that infection of the tonsil and appendix are similar and occur in a like manner, and points out that Teichmann[38] has demonstrated the presence of large lymph vessels in the appendix wall which send branches into the submucosa, forming a network about the follicles. Golubof[39] described appendicitis as a

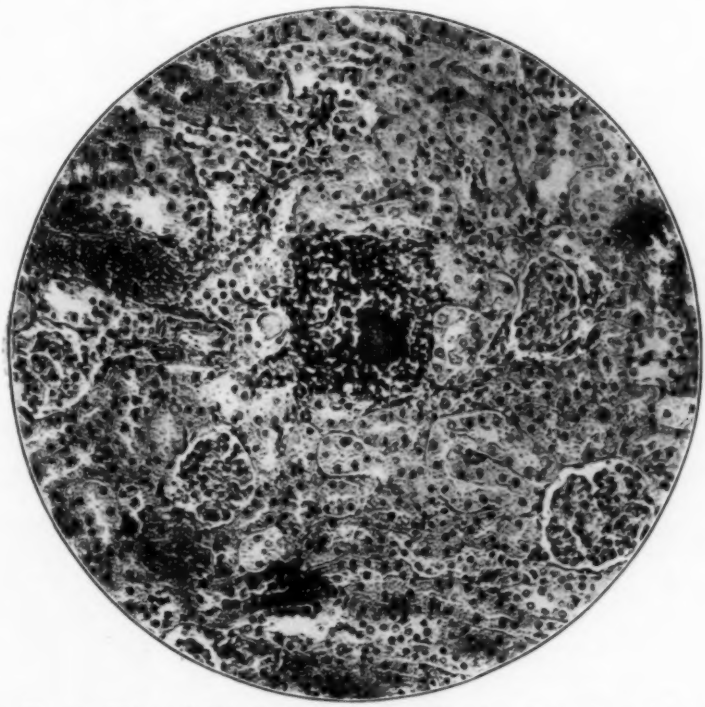


Fig. 14.—Kidney, Rabbit 64, showing embolic plugging of the glomerulus and infiltration of lymphocytes and leukocytes.

disease of the organ, arising *sui generis*, and cites in comparison follicular tonsillitis and dysentery of the large bowel. The enterogenous theory for the production of appendicitis has been further supported by Oberndorfer,[23] Albrecht,[25] Oguro,[40] Weichselbaum,[41] Beitzke,[42] Lubarsch,[43] Schmorl[44] and many others.

37. Nowicki: Virchows Arch. f. path. Anat., 1909, **195,** 175.
38. Teichmann and Nowicki: Virchows Arch. f. path. Anat., 1909, **195,** 175.
39. Golubof: Berl. klin. Wchnschr., 1897, **1,** 9.
40. Oguro: Virchows Arch. f. path. Anat., 1909, **197,** 548.
41. Weichselbaum: Dis. Verhandl. d. deutsch. path. Gesellsch., 1910, **14,** 156.
42. Beitzke: Dis. Verhandl. d. deutsch. path. Gesellsch., 1910, **14,** 155.
43. Lubarsch: Dis. Verhandl. d. deutsch. path. Gesellsch., 1910, **14,** 157.
44. Schmorl: Dis. Verhandl. d. deutsch. path. Gesellsch., 1901, **14,** 157.

Aschoff[1] recognized that in many cases tonsillitis and appendicitis occur simultaneously, one after the other, or even result one from the other. He nevertheless stated that the appendix may well be infected enterogenously from the tonsil. An important objection to the hematogenous theory, and the one which Kretz[2] admitted was the most serious, was that in none of these cases was he able to demonstrate the offending agent in the blood. This finding has been substantiated by the studies of Libmann,[45] Simmonds,[46] Lubarsch,[48] Fränkel[24] and others on the blood of patients suffering from acute appendicitis. Kretz[2] maintained that the blood infection was only transient in nature, and at the time of the general infection there was no doubt that many other organs are affected, and calls attention to the transitory bacteremias which lead to an endocarditis or to an osteomyelitis, where the condition remains mostly a solitary infection. In reply to this view of Kretz, Lubarsch[48] found with regard to the relationship between angina and appendicitis that clinical statistics do not prove a relationship between the two, in view of the extraordinary frequency of angina over appendicitis. He further goes on to say that one can hardly prove that the organisms associated with an angina are identical with those causing the appendicitis, unless the offending agent can be demonstrated in the blood, which event should be possible in at least some cases. Albrecht[25] made the very significant comment that since there are enormous numbers of streptococci which normally inhabit the entire gastro-intestinal canal, it does not follow that streptococci which can be demonstrated in the appendix necessarily come by way of the blood stream. Oberndorfer[22] pointed out the similarity between the tonsil and appendix, in that the epithelial covering of the follicles and crypts is not as efficient as in other parts of the gastro-intestinal tract, permitting a continual wandering of lymphocytes through the epithelium, which must be considered of great importance in the entrance of bacteria.

This same author remarked in regard to the Kretz theory of appendicitis that without doubt in some of the early cases a part of the follicles may be missing. There is also a pseudomembrane with necrosis at the bottom of the crypts, together with typical surface alterations. In a study of septic embolic hemorrhagic enteritis where the blood was overwhelmed with bacteria and septic emboli, he found that metastases occurred in the intestine, with a predilection for the follicular apparatus, while in the same cases the appendiceal follicles were frequently free of any inflammation. He further points out that if appendicitis is a hematogenous infection of the follicles, the remaining follicles of the small and large intestine, on account of their anatomic similarity to those in the appendix, should show similar alterations more frequently, and the fact that the follicular apparatus of the intestine of individuals dying of appendicitis is free, forms the strongest argument against the theory of Kretz.

A septic embolic infection of the appendix was not denied by Aschoff, and he spoke of its occurrence in certain cases. However, Oberndorfer[22] and Schmorl[44] have commented on the relative infrequency with which the appendix is attacked in cases of pyemia, when the other organs and upper gastro-intestinal tract developed metastatic changes. Routier[47] pointed out that the appendicitis which occurs in connection with angina, measles, varicella, parotitis, enteritis or enterocolitis, does not preclude the fact that most cases are a primary condition in the appendix. Wette[48] observed hematogenous infection of the appendix in pneumonia, angina and carbuncle, while Schrumpf[49] has described embolic plugging of the appendiceal vessels by an embolus in heart disease.

45. Libmann and Aschoff: Verhandl. d. deutsch. path. Gesellsch., 1907, **11,** 313.
46. Simmonds: Dis. Verhandl. d. deutsch. path. Gesellsch., 1906, **10,** 234.
47. Routier, Adrian: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1901, **7,** 407.
48. Wette: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1906, **16,** 303.
49. Schrumpf: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, **17,** 167.

Jores[50] has reported two cases of metastatic appendicitis developed during the course of fatal scarlet fever, where there was an infiltration in the outer coats of the organ without the mucosal changes characteristic of ordinary appendicitis. In a rabbit injected subcutaneously with urine, Gouget[51] found the development of a pyemia, with localization in the lymphoid structures, producing an abscess in spleen, suppurating mesenteric lymph nodes, and an appendix which showed nodules in the wall representing follicles crammed with leukocytes. Aschoff[1] remains of the opinion that human appendicitis is mostly a primary mucosal

Fig. 15.—Skeletal muscle, Rabbit 157, showing an area where there is proliferation of large, elongated cells between the muscle bundles, causing necrosis of the ones immediately involved. Lymphocytes and an occasional leukocyte are observed.

infection. The type of appendicitis described by Kretz[2] forms a particular variety which is easily distinguished clinically, in that the patients exhibit evidence of marked sepsis, and speedily die from other lesions following operation for the appendix condition.

More recently, in regard to the experimental production of appendicitis,

50. Jores: Verhandl. d. deutsch. path. Gesellsch., 1913, **16,** 197.

51. Gouget: Compt. rend. Soc. de biol., 1899, **1,** 631.

Poynton and Paine[52] have produced appendicitis in rabbits by injecting intravenously an organism isolated from the appendix of a patient suffering with angina and acute polyarthritis. The organism recovered from the throat had similar cultural and biologic characteristics to the one recovered from the appendix; however, this organism produced only arthritis in rabbits. Tedesco[53] found leukocytic infiltration, necroses and hemorrhage in the follicles of rabbits' appendixes when the animals were injected intravenously with staphylococcus, streptococcus and *B. anthracis*. Heile,[46] in an effort to demonstrate a specific action of bacteria on the appendix when intravenously injected, found that they did not tend to localize in the appendix more than in other organs. In this respect he was unable to corroborate the work of Adrian.[4] Again, Ghon and Namba[6] observed that rabbits injected intravenously with streptococci were very prone to show these organisms in the vessels of the appendiceal follicles, without evidence of inflammation. This fact was noted in ten of fourteen animals. However, they were not inclined to consider the lesions present as very important, in that these were in all respects similar to those which they had observed in the normal rabbit appendixes. Of fifty-five normal rabbits examined by them, they reported that thirty-seven showed gross appendiceal lesions, while in the remaining eighteen there were some which showed microscopical changes. Charrin,[29] Josué[22] and Mosny[54] have also noted spontaneous appendicitis in the laboratory animals.

From the foregoing review of the literature it is evident that for a long time there has been recognized an apparent relationship between angina and appendicitis, with the result that several investigators (Adrian[4] Kretz,[2] Poynton and Paine[52]) have endeavored to prove that appendicitis occurs by a hematogenous infection from the tonsil. Apolant[55] saw three cases of appendicitis in conjunction with angina and thought that the organisms entered the tonsil and from there sought the *locus minoris resistentiae*. The controversy between those supporting the hematogenous theory and those of the opposition in favor of the enterogenous origin of appendicitis has waged fervently without a final decision.

Recently, Rosenow[3] has published extensive results concerning the experimental production of appendicitis in rabbits, and his work has added a new conflicting attitude to the subject. Apparently following the idea of Kretz,[2] that a streptococcus from the tonsil localizes in the appendix follicles, Rosenow has still further endeavored to prove that such an organism has an elective affinity for the appendix and seeks the tissues of this organ by special predilection. Not only has this property been attributed to streptococci, but colon bacilli and staphylococci possess similar characters under the proper conditions. It has been specified that these organisms must be obtained from the appendix itself, or from the tonsils of such patients, and be cultured in a special medium containing ascites fluid. Further, the medium must be used in tall columns in order to afford a gradation of oxygen tension, which is essential for the organisms to retain the elective qualities. Several authors have reported the selective localization of organisms in tissues. Bezancon and Labbe[56] found that a staphylococcus from a cutaneous abscess which had localized in a traumatized joint, showed a

52. Poynton and Paine: Lancet, London, 1911, **2**, 1189; ibid., 1912, **2**, 439; Proc. Roy. Soc. Med., 1911, **5**, 18; Researches on Rheumatism, New York, 1914.
53. Tedesco: Arb. a. d. Geb. d. path. Anat. u. Bakter., 1908, **6**.
54. Mosny: Compt. rend Soc. de biol., 1897, **4**, 241.
55. Apolant: Therap. Monatsch., 1897, **1**, 9.
56. Bezancon and Labbe: Compt. rend. Soc. de biol., 1900, **2**, 31.

tendency to localize in the joints of other animals on intravenous injection for several generations after isolation from the traumatized joint. Forssner[57] obtained a streptococcus from an axillary abscess, and cultured it in extracts of kidney, and in kidney tissue, both in vitro and in vivo. The original organism exhibited no tendency to localize in the kidneys on intravenous injection, while the one procured after passage through kidneys presented a marked tendency to produce lesions of the kidneys on intravenous injection. After the last animal passage, the streptococcus retained this property on serum broth for four or five generations, when it was lost. Strains of *B. pestis* repeatedly grown in lung tissue show an increased ability to cause pneumonic lesions on intravenous or subcutaneous injections. In contradistinction to these facts, Irons, Brown and Nadler[58] were unsuccessful in attempts to obtain a return of invasive power for tissues of the eye in strains of streptococcus which had lost it, by growing the organisms in the living eye.

From the foregoing evidence it is difficult to conceive in what manner the tonsils act to impress such varied affinities on organisms, and how a transudate from the peritoneum may serve to preserve these qualities.

We wish to call attention to the fact that the medium used for this work was dextrose serum broth, used in 150 c.c. amounts, in Erlenmeyer flasks. In 125 rabbits injected intravenously with a variety of organisms cultured by this method, gross hemorrhages were noted in the appendix sixty-two times. The fact that the organisms injected can frequently be demonstrated in the hemorrhages which occur in this organ, is not conclusive evidence that these organisms select the tissues of the appendix with a predilection. When a gross hemorrhage takes place into the tissues of an organ, whatever material is in the blood will be carried into the involved area. If the blood is overwhelmed with bacteria, many of the small vessels in various parts of the body become plugged. This plugging of small vessels forms a mechanical obstruction to the circulation, and the delicate capillaries are very apt to rupture, followed by hemorrhage, which must be composed of all the constituents of the blood. The frequency with which hemorrhage and bacterial emboli are observed without the presence of an inflammatory reaction, suggests that a mechanical factor must be considered as well as the direct action of the organisms and their toxins.

We have also observed that the thymus, lymph glands of the mesentery, of the inguinal region, glands about the head of the cecum, and also Peyer's patches, were commonly affected in conjunction with hemorrhages distributed variously throughout the organs of the body. From these findings and the evidence which we are able to gather from the literature it would appear that the rabbit is peculiarly prone to exhibit alterations in his lymphoid apparatus when organisms gain entrance to his blood stream. It is a generally recognized fact that

57. Forssner, Irons, Brown and Nadler: Jour. Infect. Dis., 1916, **18,** 315.
58. Irons, Brown and Nadler: Jour. Infect. Dis., 1916, **18,** 315.

there is no tissue or organ of the human body immune to invasion by streptococci. This organism is not alone confined to the human species, but is also found associated with diseased conditions in domestic animals. Streptococci have been indiscriminately found associated with erysipelas, puerperal fever, septic sore throat, scarlet fever, malignant endocarditis, polyarthritis, streptococcic pneumonia, purulent pleurisy, summer diarrhea of children, together with wound infection and sepsis, with a host of other conditions to which human beings are susceptible. In animals they have been found with spontaneous infections, puerperal fever, contagious coryza, pleuropneumonia of horses and certain inflammatory diseases of the udders of cows. Erysipelas has been induced experimentally with matter taken from wounds, from throats in angina and from the uterus in puerperal fever. Further, as Vaughan[59] has said, all these and many other diseases are due to the same organism, and are mutually convertible one into another. In this connection, Poynton and Paine[52] have produced arthritis in rabbits with streptococci from the throat, feces and urine.

If appendicitis is a local manifestation of a general infection due to a special organism, it should be possible to demonstrate the organism in the blood at some time during the course of the disease. Until this fact has been definitely established for appendicitis, not including the pyemic type of the disease, one can little hope conclusively to prove that a particular organism is at fault. Kotzenberg,[60] in a study of the opsonic index of appendix patients, found that their serums reacted equally well for streptococci, staphylococci and *B. coli*. Further, the fact that a variety of different organisms have been associated with changes in rabbits appendixes, tends to indicate that a special organism has not yet been found. The production of appendicitis in animals by the intravenous injection of large doses of vigorous bacteria cannot be considered as an indication that these organisms attack the human appendix by way of the blood. Even in the most extreme cases, where the blood is overwhelmed with bacteria, the appendix is only occasionally involved (Oberndorfer,[22] Albrecht[25]). The condition produced in the appendix of the rabbit is primarily intramural, and is the analogy of a particular type of human appendicitis observed in pyemia. It cannot be compared with the common type of appendicitis as described by Aschoff.[1] At present all authors are agreed that infection is requisite in the production of appendicitis. However, the widely divergent theories which have been advanced, including stasis (Dieulafoy), the hematogenous (Kretz[2]) and alimentary theories (Aschoff[1]), the idea of the similarity between the tonsil and appendix (Sahli[16]), and lastly,

59. Vaughan: Commemoration Volume, 1915, p. 107.
60. Kotzenberg and Much: Deutsch. med. Wchnschr., 1909, **5**, 201.

the effect of fecal concretions (Sprengel[61]), indicate that the appendix is the subject of many insults. Further, the comparison of the lesions which occur in the appendixes of animals in this type of experiment with human appendicitis, should be made with extreme caution, as the disease in the animal is produced by very vigorous methods, and never assumes the character of the disease as it is observed in man. We feel obliged to protest against the idea that any organism possesses a peculiar affinity for any given organ when the same organism shows a capacity for the invasion of other organs in a very appreciable proportion of experiments. As the result of our study of the literature, and our own experimental work, we find little evidence to support the belief that appendicitis in the human subject is ordinarily caused by a blood infection.

This work was carried out under the direction of Dr. John A. Hartwell, to whom I am much indebted for advice and assistance.

61. Sprengel and Oberndorfer: Ergebn. d. allg. Pathol., 1909, **13**, 527.

TRANSIENT HEART BLOCK — ELECTROCARDIOGRAPHIC STUDIES *

EDWARD B. KRUMBHAAR, M.D.
PHILADELPHIA

The study of the heart beat by means of modern instruments of precision, such as the polygraph and the string galvanometer, has revealed the fact that the graver forms of cardiac arrhythmia, as heart block and auricular fibrillation, are much more common than was previously suspected. It has also been recognized that such arrhythmias as paroxysmal tachycardia, flutter and premature contractions (extrasystoles), are notoriously transient in most cases, but until very recently heart block (especially complete block) and auricular fibrillation were looked on as being nearly always permanent conditions due to extensive organic changes. In 1910, however, I[1] was able to show that complete heart block may exist for years without demonstrable lesion of the bundle of His at autopsy, and similar cases have occasionally been reported since that time (see Ref. 8). In the case of auricular fibrillation, I have recently shown[2] that transient attacks are not only fairly common, but may be divided into three well-defined groups, whereas transient heart block occurring during an acute infection (Naish and Kennedy[3]), or as the result of digitalis medication (Hewlett[4]), is now an even better recognized condition. It is to such cases that Hart[5] has applied the term "functional heart block," "not because we believe organic changes are absent, but because such changes are of such a moderate degree or are of such a nature that by the administration of drugs the evidence of functional abnormalities can be considerably modified." With these reservations the term is a serviceable one, and yet it would be unfortunate to distract attention too much from the myocardial damage, whether acute or chronic, slight though it may be, which undoubtedly underlies the majority of such cases. The following cases illustrate different types of this rather complex condition.

---

* Submitted for publication Dec. 16, 1916.

* From the Medical Division and the Pepper Clinical Laboratory, Hospital of the University of Pennsylvania.

1. Krumbhaar, E. B.: Adams-Stokes Syndrome, with Complete Heart Block without Destruction of the Bundle of His, THE ARCHIVES INT. MED., 1910, **5**, 583.

2. Krumbhaar, E. B.: Transient Auricular Fibrillation, THE ARCHIVES INT. MED., 1916, **18**, 263.

3. Naish, A. E., and Kennedy, A. M.: Heart Block in Acute Rheumatic Carditis, Lancet, London, 1914, **2**, 1343.

4. Hewlett, A. E.: Digitalis Heart Block, Jour. Am. Med. Assn., 1907, **49**, 47.

5. Hart, T. S.: Functional Heart Block, Am. Jour. Med. Sc., 1915, **149**, 62.

I. Transient Partial A-V Block in Acute Rheumatic Carditis.—The case selected as an example of this type of block was observed during a recurrence of acute articular rheumatism. It illustrates the temporary nature of the block, a parallelism between the block and the degree of rheumatism, the type of ventricular arrhythmia produced, and the influence of vagus stimulation and inhibition on the disturbed mechanism.

Case 1.—M. C., single, white, actress, aged 34, was admitted to the medical service of the University Hospital, Feb. 19, 1915, complaining of "an acute attack of rheumatism" of two weeks' duration, following tonsillitis and exposure. Severe pains occurring simultaneously in several joints and in most of the muscles of the body, were partially relieved by salicylates, but still persisted in the back, sides and arms. The wrist and elbow of the left arm were painful, tender, red and swollen.

When 16 years old the patient had had a severe attack of rheumatic fever, with cardiac complications, and since then she had had several recurrent attacks, and had experienced more or less palpitation and dyspnea. Her profession exposed her to inclement weather and she was addicted to excess in

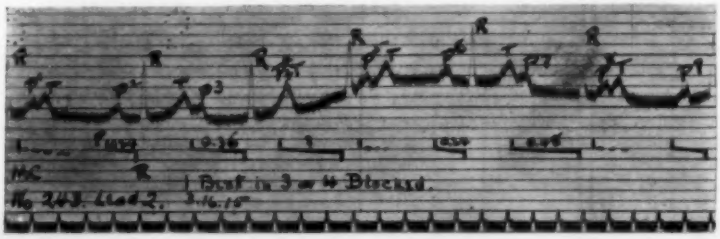


Fig. 1.—Case 1. Electrocardiogram (Lead 2) of M. C., showing partial heart block. It will be noticed that the first, fifth and eighth P waves fail to be followed by a ventricular complex. After each such "dropped" beat, the succeeding P-R interval is almost within normal limits, but the P-R interval of each succeeding cycle is lengthened until another "dropped" beat occurs. In this, as in other electrocardiograms of this series, platinum wire strings were used with resistances varying between 3,000 and 4,000 ohms. The tension of the string was so standardized that a change in potential of 1 millivolt caused a deflection of 1 cm. As the string could not be standardized with the patient in circuit, 1,400 ohms were added as an arbitrary equivalent of the patient's resistance. Time intervals are expressed by a Jaquet time marker in fifths of seconds, and occasionally by vertical lines indicating $\frac{1}{5}$ and $\frac{1}{25}$ second.

eating and late suppers, with immoderate indulgence in beer, whisky and coffee. Several other members of the family suffered with "rheumatism." At no time during the present illness had the patient received any digitalis or allied drugs.

Physical Examination and Course of Illness.—The condition of the muscles and joints corresponded to the description given by the patient. Dental caries, pyorrhea alveolaris, general nervousness and the state of the heart were the other points requiring consideration. The heart dulness began above at the third rib, the right border was 3 cm. to the right of the midsternal line, and the left border 12 cm. to the left of the midsternal line and 2 cm. outside the midclavicular line. There was a well-marked apex beat in the fifth space, 2 cm. inside the limit of dulness. At the apex was heard a loud, harsh, blowing systolic mur-

mur, largely replacing the muscle sound and transmitted to the axilla. The second pulmonic sound was slightly accentuated. The radial pulses were equal, synchronous, regular, of moderate quickness, volume and tension, and not sclerotic. The patient refused to have the routine electrocardiogram taken at this time. Blood pressure: 110 systolic, 70 diastolic; hemoglobin, 70 per cent.; red blood count, 4,260,000; leukocytes, 13,200. The urine contained a trace of albumin, leukocytes, mucus, epithelial cells and no casts.

In short, the case was that of an ordinary recurrent attack of acute articular rheumatism in a patient suffering with chronic mitral endocarditis (regurgitation). During the first week of her stay at the hospital an extension to other joints and an increase in the temperature indicated that the administration of salicylates should be increased. Following 1.5 gm. of sodium salicylate every hour the temperature was quickly reduced so that the dosage was reduced to 0.3 gm. every fourth hour. Four days later, full doses were resumed in

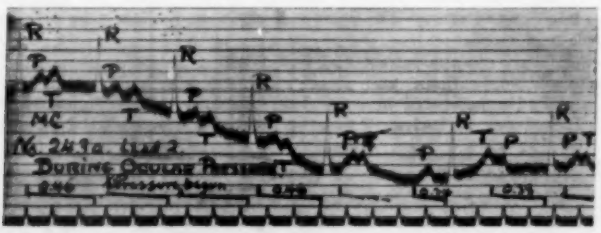


Fig. 2.—Case 1. Electrocardiogram (Lead 2) of M. C., showing the effect of vagus stimulation, by ocular pressure, on partial heart block. Note in the first four beats that although the P-R interval is greatly prolonged, it is equal in all, and no beat fails to provoke a ventricular response. After the fifth P wave is blocked, there is a return to gradual prolongation of the P-R interval.

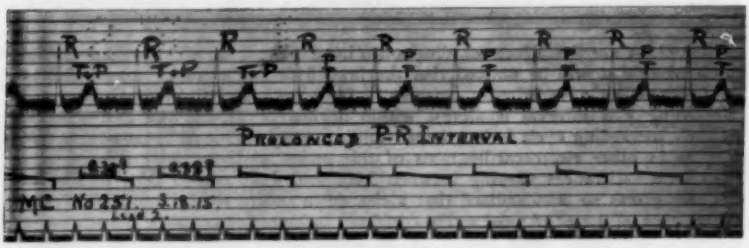


Fig. 3.—Case 1. Electrocardiogram (Lead 2) of M. C., after the administration of 1 mg. atropin. No beats are blocked, and the P-R intervals are equal. They are so long, however, that the P wave is superimposed on the preceding T.

response to higher fever and a new involvement of the right wrist. The patient again responded to treatment after four days, but the medication was continued for another week, at the end of which time the heart rate dropped suddenly from 90 to 44, the sounds became of poorer quality and the second pulmonic sound was occasionally reduplicated. The cardiac dulness was found to be 1 cm. wider, both to right and left, than on previous examination. Although no note of cardiac arrhythmia was made until one week later, on which date the record of Figure 1 was taken, it is most probable that the arrhythmia began at the time the first drop in rate was noted. The electrocardiogram shows a varying degree of partial block. In Lead 2 there is a gradual increase

of the P-R interval, until, after about every fourth auricular impulse, the ventricle fails to respond. Following such a "dropped" beat, the P-R interval is shortened and a similar cycle recommended. In Leads 1 and 3 the degree of block is different, there being a 2:1 rhythm in which every other auricular contraction fails to be followed by a ventricular contraction. These findings confirmed polygraphic tracings taken on the same day. Contrary to expectation, during vagus stimulation by ocular pressure the degree of block was slightly less. The "dropped beats" occurred as before, but with lesser frequency, and the preceding P-R intervals, though prolonged for a short time to more than 0.4 second, were all equal for several beats. Electrocardiograms taken on the next two days revealed the same state of affairs. At this time, 1 mg. of atropin administered hypodermically proved sufficient temporarily to prevent the "dropping" of beats. The P-R interval, however, remained prolonged (0.38 second) and there was no appreciable rise in the auricular rate. After four days

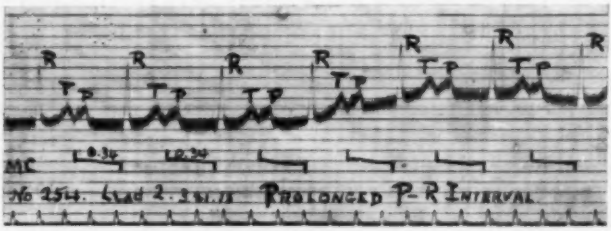


Fig. 4.—Case 1. Electrocardiogram (Lead 2) of M. C., three days later after the administration of 1 mg. of atropin. The slightly slower rate (longer diastole) and shorter P-R interval allow the P wave to be distinguished from the preceding T.

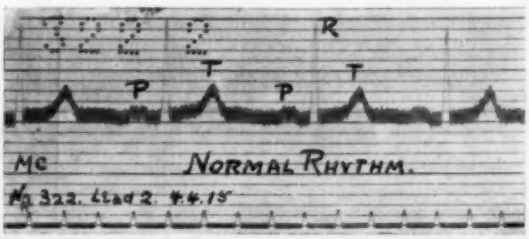


Fig. 5.—Case 1. Electrocardiogram (Lead 2) of M. C., showing normal rhythm and normal P-R interval.

of atropin medication (0.3 mg. hypodermically three times a day), the rhythm remained regular for several days; the P.R interval was not as much prolonged as before, and the P wave no longer coincided with the preceding T. In other words, although the block was not due to medication, and from the nature of the disease process was presumably due to an acute myocarditis involving His' bundle, nevertheless the administration of atropin was sufficient to prevent any beats being "dropped." Does this indicate that the vagus as well as the diseased bundle was a factor in the block, or does it indicate that atropin exerts a direct dromotropic effect on His' bundle? Two days after this tracing was taken, the acute arthritis recurred in one finger, together with fever and episcleritis of the right eye. Electrocardiograms at this period showed the same condition of partial block as before described. Atropin medication was again

begun, together with atophan. In four days the temperature had returned almost to normal, the patient was without pain, and the cardiac rhythm was regular. From that time until the patient's discharge from the hospital, electrocardiograms showed not only a regular rhythm, but a normal P-R interval (0.19). A slight recurrence of pain, swelling and redness in two knuckles of the left hand, with a rise of 1 degree in temperature, did not have any effect on the cardiac rhythm, and the patient progressed to an uninterrupted recovery from the acute rheumatism. It was later ascertained, however, that the patient died, within two months of the time of her discharge, of acute yellow atrophy of the liver. In the terminal illness the heart continued regular at the rate of 100 beats per minute. Necropsy was refused.

DISCUSSION

During an attack of recurrent acute articular rheumatism in a patient suffering with chronic mitral endocarditis, cardiac hypertrophy and probably some chronic myocarditis, there was presumably superimposed an acute myocardial involvement of His' bundle. This was extensive enough to lower the conductivity of the bundle sufficiently to cause partial heart block. Vagus stimulation failed to change the stage of heart block, but did slightly change its character. After the administration of atropin, impulse conduction was delayed but no longer blocked. Coincident with improvement in the other rheumatic symptoms, the block disappeared, to reappear again with a recrudescence of symptoms. At this time, during the administration of atropin, the dropped beats disappeared and the P-R interval became normal. A third minor recurrence of rheumatic symptoms, however, failed to affect the now normal heart rhythm, which continued normal as long as the patient was under observation. The administration of salicylates cannot be considered to have had any connection with the production of the block; not only because this class of drugs is not considered to have any effect on conductivity, but also because the degree of block in this case usually varied inversely with the degree of salicylic medication.

It is of interest that although the block was presumably of myocardial origin, it was nevertheless influenced by factors affecting the vagus, and thus indirectly affecting the damaged conductive system.

II. Transient Complete A-V Block Due to Digitalis.—Transient digitalis block of lesser degrees is not an uncommon condition, but a transient complete block, especially when following relatively small doses of digitalis, must be considered as very unusual.

CASE 2.—M. F., married, Irish, hospital orderly, aged 65, had been suffering for over a year with attacks of giddiness, weakness, loss of vision, and on two or more occasions apoplectiform attacks, which lasted some hours, but were not followed by any hemiplegia. On one of these occasions he was admitted to this hospital for one week, but no bradycardia or arrhythmia was observed, although tincture digitalis (0.32 c.c. three times a day) was given for six days. His past and family histories are unimportant, except for a life of hard work and exposure, with moderate use of alcohol, tobacco, tea and coffee.

Physical Examination and Course.—On the present admission, Jan. 11, 1916, the following pertinent signs were observed: blood pressure, systolic, 130, diastolic, 70; marked pyorrhea; emphysematous chest; cardiac dulness: right border 4 cm. from midline, left border 14.5 cm. from midline, outside of left midclavicular line; apex beat neither visible nor palpable; heart sounds weak, no murmurs; blood and urine normal.

Tincture of digitalis (0.65 c.c. three times a day) was given for two days, when it was noticed that the patient's pulse had become slow (38 beats per minute) and irregular. It was afterward ascertained that previous to admission, the patient had taken 0.3 c.c. of the tincture of digitalis four times a day for four days, thus making a total dosage of only 8.7 c.c. of the tincture spread over six days. An electrocardiogram taken at this time showed a complete block with

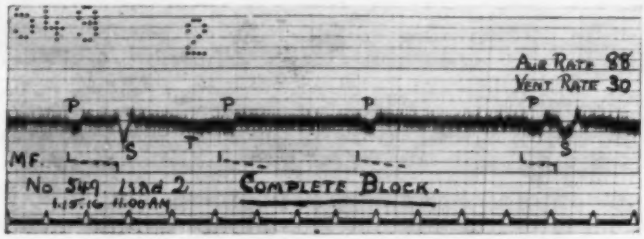


Fig. 6.—Case 2. Electrocardiogram (Lead 2) of M. F., showing complete heart block. Note that there is no constant relation between the occurrence of P and S (ventricular complex); although P twice falls before S, the P-R interval is different in both cases. The complete dissociation is even more obvious when the whole length of film is consulted. Note that the P waves are inverted and the ventricular complex of peculiar shape.

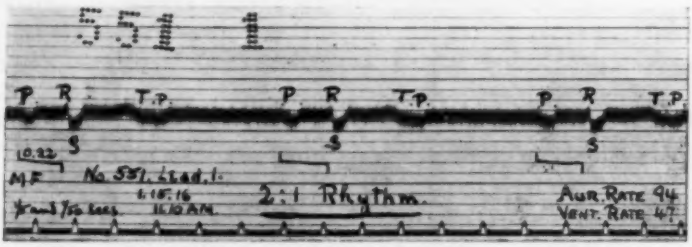


Fig. 7.—Case 2. Electrocardiogram (Lead 1) of M. F., showing partial heart block (2:1 rhythm) after the administration of 2 mg. of atropin.

a varying form of ventricular complex (auricular rate, 88; ventricular rate, 30). Not only were the ventricular deflections very small, but the heart sounds were quite inaudible. Immediately after this record was made, 2 mg. atropin were given hypodermically. The pulse rate rose in ten minutes to 50, and an electrocardiogram showed that the complete block had been replaced by a 2:1 rhythm.[6] The P-R interval was longer than normal (0.22 second). One-half hour later,

6. This might be interpreted as a normal rhythm, the second P wave being considered as part of a long diphasic T; but such an interpretation is highly improbable, as it would presuppose not only a very unusual form of T wave, but also the very slow auricular rate of 47.

complete block was reestablished (auricular rate, 100; ventricular, 46). During all this period the patient was quite comfortable, resting quietly in bed. Digitalis medication was stopped and thirty-six hours later the pulse rate had risen to 70, about which point it stayed during the rest of the patient's stay in the hospital. The P-R interval, however, remained prolonged (0.20 second), and was not changed by increasing the heart rate with atropin. When seen two months later, the patient had had no more "attacks," though he was still somewhat "shaky" in his legs. Electrocardiogram showed a normal rhythm, but the P-R interval still remained long.

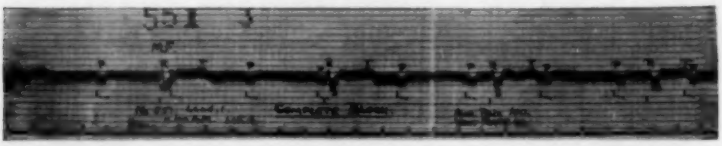


Fig. 8.—Case 2. Electrocardiogram (Lead 1) of M. F., showing the return to complete heart block, forty minutes after the administration of atropin. Note that P occurs at regular intervals but without relation to, and occasionally superimposed on, the ventricular complex (R S).

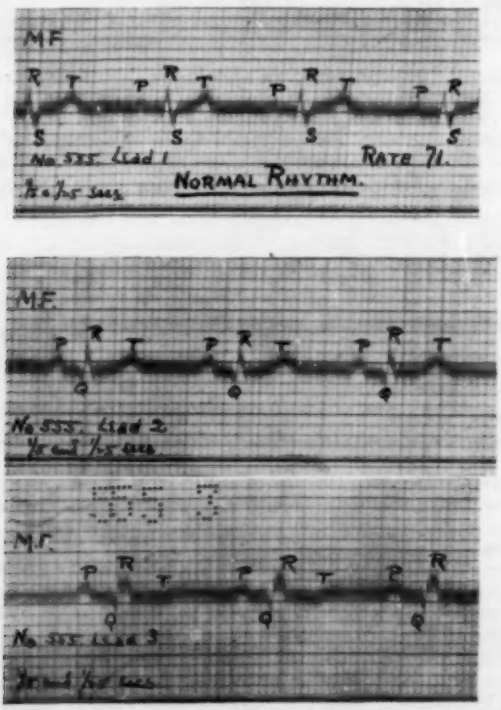


Fig. 9.—Case 2. Electrocardiogram of M. F. (three leads). Normal rhythm. Note also that the P waves are no longer inverted and that the ventricular complexes are of normal shape.

DISCUSSION

In an old man suffering from chronic myocardial degeneration and arteriosclerosis, and subject to spells of weakness and unconsciousness, moderate digitalis dosage for less than a week, brought on a transient, complete A-V heart block, with varying types of ventricular complexes. This was temporarily relieved by atropin, and disappeared spontaneously thirty-six hours after the digitalis was stopped. Although digitalis was obviously the determining factor in the causation of the block, it is but fair to assume that degenerative changes in the fibers of His' bundle contributed to the easier production of the digitalis effect. The temporary cessation of the block after the administration of atropin offers an interesting comparison with the first case. If in that case, as seems probable, atropin exerted a direct dromotropic effect on His' bundle, one might assume that here also the atropin effect may have been obtained partly through direct action on the bundle, although on account of the obvious importance of digitalis effects, the paralyzing action on the vagus must, of course, also be taken into account. The varying forms of ventricular complexes during the digitalis period are of the same kind as previously described by Cohn,[7] Oppenheimer and Williams[8] and Christian.[9]

III. Development of Defective Conductivity of Right Branch of His' Bundle.—The subject of defective conductivity in one or other branch of His' bundle has been thoroughly presented by Carter[10] and Matthewson[11] from the clinical, and by Eppinger and Rothberger[12] from the experimental, side. At least one case is on record also in which transient block occurred in the right branch of His' bundle during a febrile attack (Lewis[13]), and Carter cites instances in which, as in the present case, the bundle branch block is complicated by extrasystoles. The following case, however, is unique in one particular,

7. Cohn, A. E.: A Case of Transient Complete Auriculo-Ventricular Dissociation, Showing Constantly Varying Ventricular Complexes, Heart, 1913, **5,** 5.

8. Oppenheimer, B. S., and Williams, H. B.: Prolonged Complete Heart Block without Lesion of the Bundle of His and with Frequent Changes in the Idioventricular Electrical Complexes, Proc. Soc. Exper. Biol. and Med., 1913, **10,** 86.

9. Christian, H. A.: Transient Auriculoventricular Dissociation with Varying Ventricular Complexes Caused by Digitalis, THE ARCHIVES INT. MED., 1915, **16,** 341.

10. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Ventricular Bundle, THE ARCHIVES INT. MED., 1914, **13,** 803.

11. Matthewson, G. D.: Lesions of the Branches of the A-V Bundle, Heart, 1913, **4,** 385.

12. Eppinger, H., and Rothberger: Ueber die Folgen der Durschneidung der Tawaraschen Schenkel des Reizleitungssystem, Ztschr. f. klin. Med., 1910, **70,** 1.

13. Lewis, T.: Certain Physical Signs of Myocardial Involvement, Brit. Med. Jour., 1913, **1,** 484.

that the earliest record was taken at the time when the branch block was apparently in the process of formation, and opportunity was offered to follow the case until the block was permanently established.[14]

CASE 3.—F. L., man, married, retired, aged 76, had been under observation for ten years for symptoms suggesting arteriosclerosis and myocardial weakness (precordial pains, especially after meals, dyspnea on exertion, enlarged liver, occasional cough). After exercise the precordial oppression increased and the pain occasionally radiated down either arm. The pulse had always been slow (55 to 65), the blood pressure was but moderately increased (average examples are: in 1912, systolic, 130; diastolic, 80; in 1913, 135 and 90; 1914, 155 and 80; 1915, 155 and 80; 1916, 155 and 70). A systolic murmur and an occasional slight arrhythmia had been noticed in the previous two years. The heart was enlarged to the left, the supracardiac dulness increased and the lungs emphysematous. The blood and urine were negative.

Except for an attack of biliary obstruction twenty-five years previously, and a tendency to constipation and flatulence, the past medical history is negative. For years the patient had smoked six to twelve cigars a day and indulged moderately in whisky. No venereal disease. Family history negative.

One month after the last electrocardiogram was taken, the patient died suddenly of acute cardiac failure. No necropsy was had.

Examination and Course.—In the first electrocardiogram, taken in January, 1915, although most of the complexes are of the type indicating left ventricular preponderance, occasionally one appears with the characteristic form of defective branch conduction, that is, notching and prolongation of the Q-R-S interval to more than 0.1 second. These occur as premature contractions. (The electrocardiogram is further complicated by the appearance of occasional auricular extrasystoles.) One month later almost all complexes were of this form and present typical examples of defective conductivity of the right branch of His' bundle. They are no longer premature. The auricular extrasystoles were still present. The P-R interval also had been prolonged from 0.20 second to 0.25 second. As the patient had been taking moderate doses of digitalis during this month, it was thought that a digitalis block might have been present, but 2 mg. of atropin hypodermically only raised the rate from 63 to 105 without altering the block. It became impossible to make further studies at this time, as the patient was living in another city. One year later, however, he returned, having been given digitalis for one month previously, and again the branch defect was found, this time in every complex. In fact, the electrocardiogram taken at this time was almost the counterpart of the one taken the year before, as far as the blocked complexes were concerned. All digitalis medication was stopped, but electrocardiograms taken on several occasions after this, on one occasion after one week's administration of atropin ($\frac{1}{150}$ grain by mouth four times a day) showed the same condition of defective conductivity to be constantly present. The patient felt badly when digitalis was given and was subjectively improved during the administration of atropin.

DISCUSSION

A man 76 years of age, suffering from arteriosclerosis, cardiac hypertrophy and chronic myocarditis, and mild anginoid attacks, was

14. Oppenheimer, B. S., and Rothschild, M. H.: Abnormalities in the Q R S Groups of the Electrocardiogram Associated with Myocardial Involvement. Soc. Exper. Biol. and Med., Dec. 20, 1916. These authors have pointed out that electrocardiograms can be produced by lesions involving terminal fibers of a branch of His' bundle, and claim a different picture for a block of the main stem of a branch.

examined electrocardiographically to determine the form of arrhythmia that was present. This was found to be due to occasional auricular extrasystoles, and anomalous ventricular beats, due to deficient conductivity in the right branch of His' bundle. One month later, almost all complexes were of this type, but no longer premature. The P-R interval was prolonged to 0.25 second, and the condition was not altered

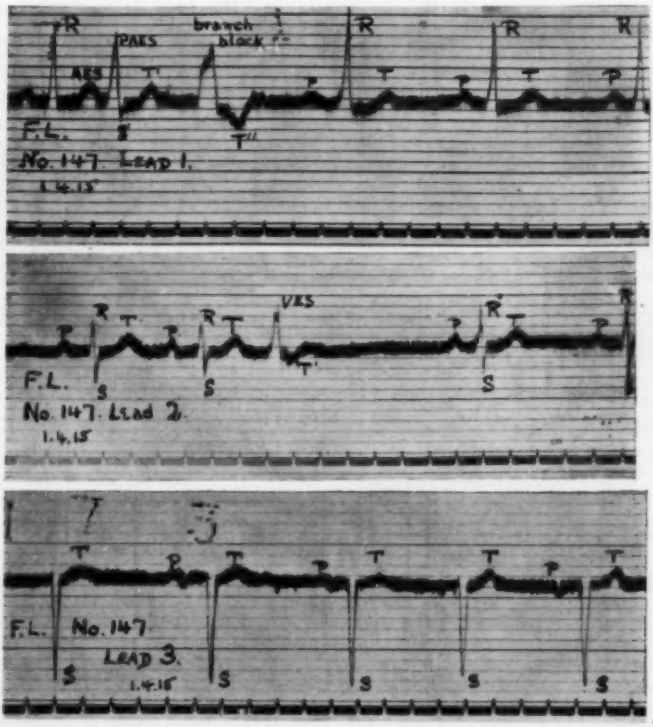


Fig. 10.—Case 3. Electrocardiogram of F. L. (three leads). Note that although most of the complexes are of the type indicating preponderance of the left ventricle, one in Lead 1 occurring prematurely is notched and broader (that is, slower). In the light of future records this is undoubtedly due to the impulse being blocked in the right branch of His' bundle. It is preceded by an auricular extrasystole and in Lead 2, an isolated ventricular extrasystole (probably of the branch block type) occurs. For purposes of reproduction, this print and the Q R S group of a few others have been retouched.

by atropin. One year later, in spite of long continued abstinence from digitalis, the same condition of defective conductivity was found to be present. It is, therefore, safe to assume that the defective conductivity (probably caused by the chronic myocarditis) was developing when

the patient was first seen and later became permanent, and it is important to note that the block developed without clinical symptoms or signs other than those revealed by the string galvanometer.

IV. Transient Prolongation of P-R Interval (of Unexplained Origin), Associated with Paroxysmal Tachycardia.—Prolongation of the P-R interval as a result of digitalis medication is too common a condition to require further comment. In the present instance, however, in a healthy young adult who also had attacks of paroxysmal tachycardia, the condition had occurred on at least two occasions in the absence of digitalis medication, or in fact of any other adequate cause.

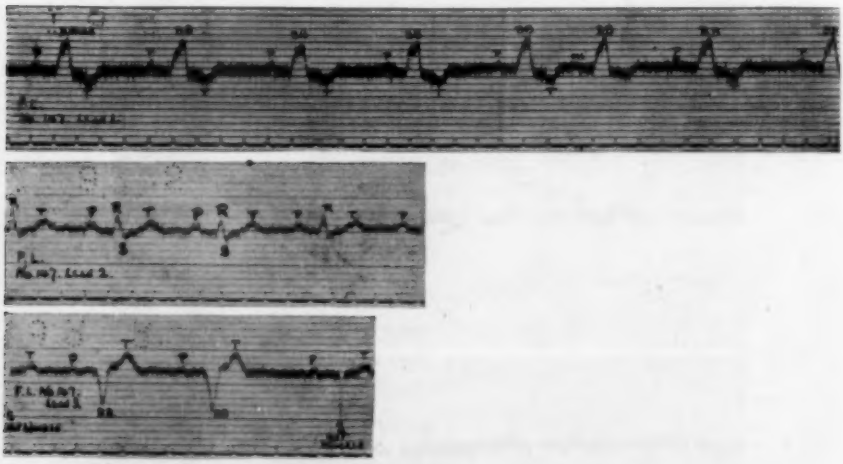


Fig. 11.—Case 3. Electrocardiogram of F. L. (three leads), showing defective conductivity (block in right branch of His' bundle) in almost all leads. Note that in Lead 3, two beats (S) are of the original type; all the others are notched and slow. An auricular extrasystole in Lead 1 is followed by the same kind of complex.

Case 4.—H. W. B., medical student, aged 23, was admitted to the student's ward of the University Hospital, Feb. 2, 1915, suffering from an attack of acute tonsillitis, vague joint pains and very rapid heart rate (over 150). These conditions subsided, after one day's rest in bed, with such suddenness that a diagnosis of paroxysmal tachycardia was made. After the paroxysm the pulse varied between 72 and 100.

The past history showed that the patient had had a slight attack of rheumatic fever when 10 years old, had had frequent attacks of tonsillitis since that time, and had a mild, chronic, atrophic nasopharyngitis. He smoked four or five cigarets and drank two cups of coffee a day, but took no alcohol. He denied any history of venereal disease. He was distinctly neurotic, with vasomotor instability, and at the time of admission had been studying unusually hard and worrying over examinations. His health was otherwise excellent

and he could undertake violent exercise without any cardiac distress, further than that he "notices that he has a heart."

Examination and Course.—The first electrocardiographic examination taken the day after admission, when the patient was feeling well, revealed a regular slow rhythm, normal in every respect except for the greatly prolonged P-R interval (0.36 second). On account of the recent history of tachycardia, however, another record was taken immediately after exercise. After climbing two flights of stairs, a task sufficient to raise a normal heart rate from 72 to 96, the patient's heart rate was raised from 78 to 108. An electrocardiogram

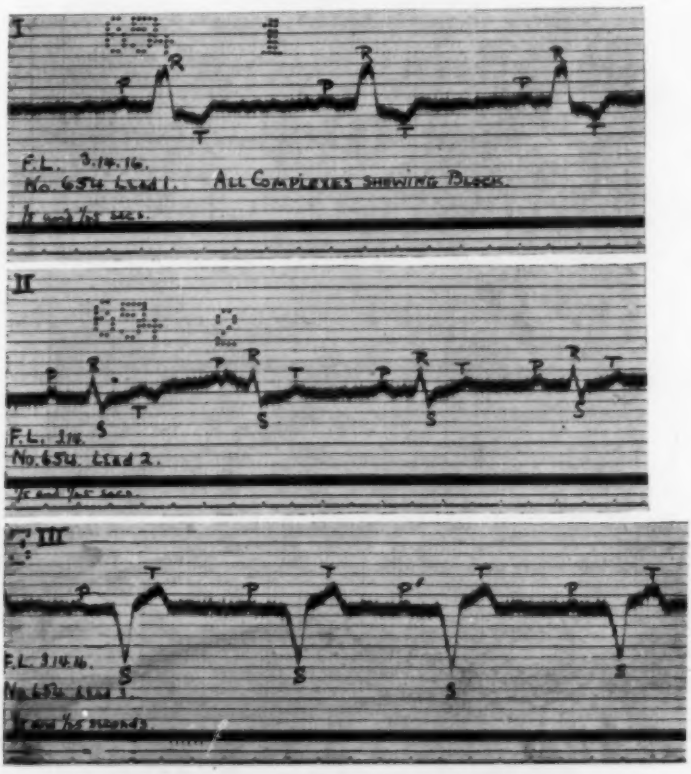


Fig. 12.—Case 3. Electrocardiogram of F. L. (three leads), showing defective conductivity (block of right branch of His' bundle) constant in all complexes.

taken at this time showed disappearance of the P wave (fused with the preceding T) during the rapid period (chiefly due to the prolonged P-R interval), and fortunately also caught the sudden cessation of the paroxysm, with reappearance of P. (Change in rate from 100 to 67.) (This record (Fig. 13) is almost a duplicate of figure 62 in Lewis' Clinical Electrocardiography). A record was then taken during forced respiration, which produced an arrhythmia, due both to sinus arrhythmia and to changes in the P-R interval. Atropin

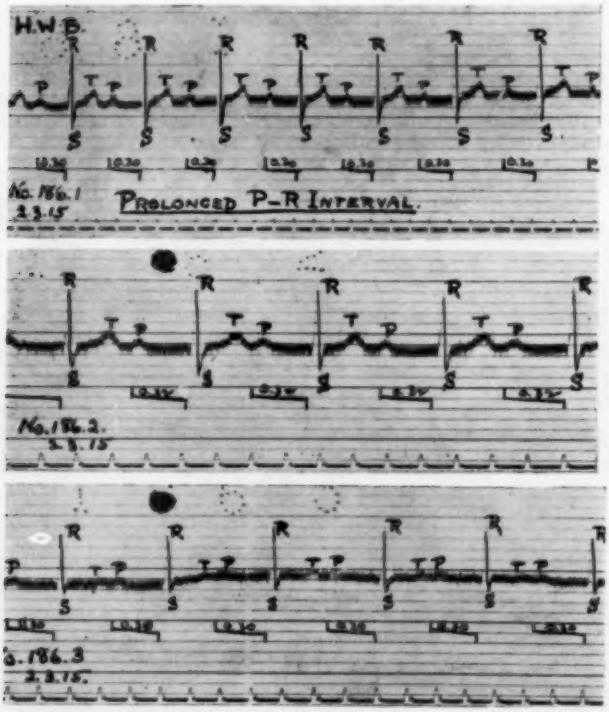


Fig. 13.—Case 4. Electrocardiogram of H. W. B. (three leads), showing prolongation of the P-R interval, earliest stage of heart block. Note that except for the greatly prolonged P-R interval (0.30 second) the record is normal.

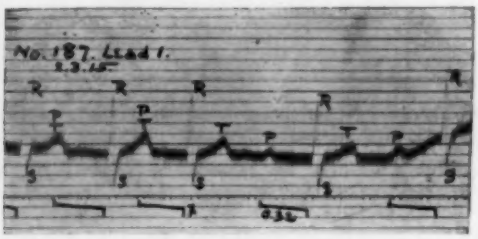


Fig. 14.—Case 4. Electrocardiogram of H. W. B. (Lead 1), showing termination of an attack of paroxysmal tachycardia. The P wave during the paroxysm is superimposed on the preceding T, so that it is apparent that the P-R interval remains prolonged during the paroxysmal period. The fact that this combined wave is higher than the single T wave of the normal period is an indication that the P waves of the paroxysm were upright, and therefore arose at or near the sinus.

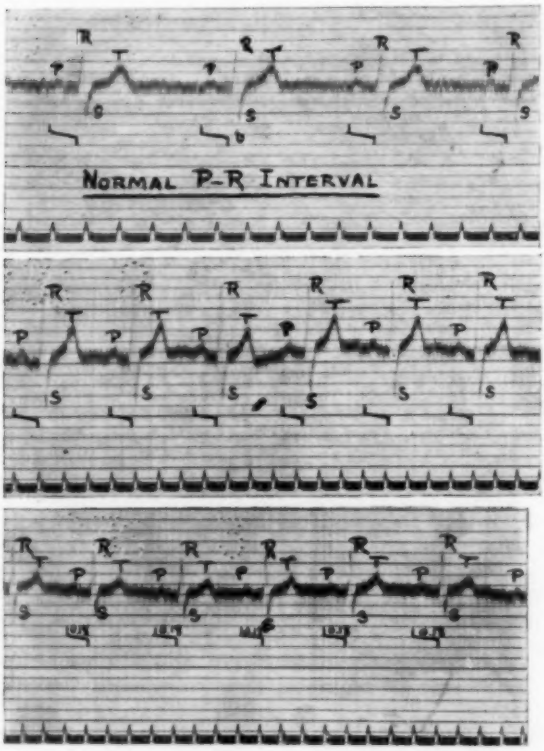


Fig. 15.—Case 4. Electrocardiogram of H. W. B. (three leads) showing normal rhythm with normal P-R interval (0.18 second).

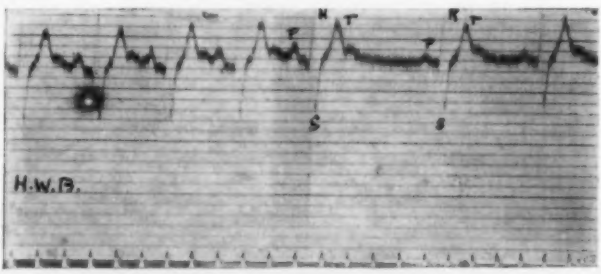


Fig. 16.—Case 4. Electrocardiogram of H. W. B. (Lead 2), showing termination of an attack of paroxysmal tachycardia with retention of the normal P-R interval. Note that the P wave is upright throughout.

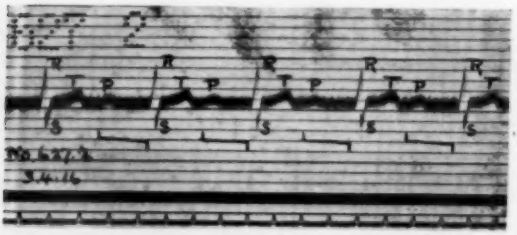



Fig. 17.—Electrocardiogram of H. W. B. (three leads), showing prolongation of the P-R interval one year later (similar to Fig. 12).

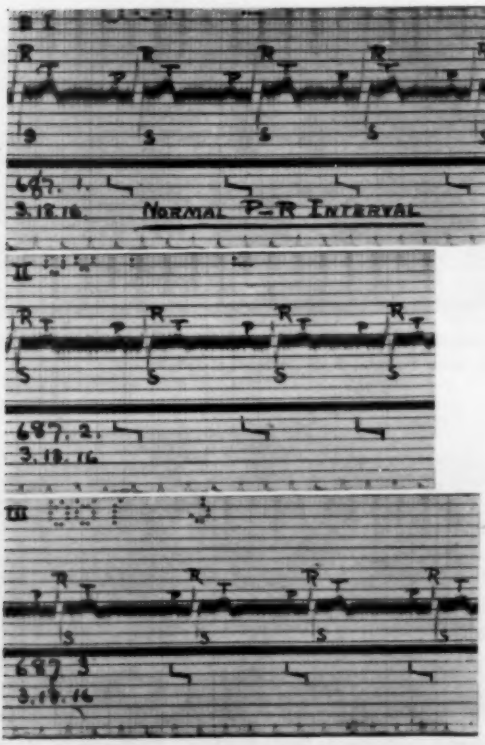


Fig. 18.—Electrocardiogram of H. W. B. (three leads), showing normal P-R interval, two weeks later than Figure 17 (similar to Fig. 14).

(2 mg. hypodermically) produced a tachycardia similar to that produced by exercise, raising the pulse rate from 85 to 128.

One month later, no medicine having been taken since leaving the hospital, an electrocardiogram showed that the P-R interval was now within normal limits (0.18 second). Except for an accentuation of S and T in all leads, the record is otherwise the same as on the previous examination. As the prolonged P-R interval produced no other signs or symptoms, the patient was ignorant of when the change to normal rhythm occurred. Exercise, however, produced a tachycardia similar to that first observed, except that as the P-R interval remained normal P and T were no longer fused. The rapid heart rate slowed to a normal rate during one cycle, as on the previous occasion. The post paroxysmal pause is longer than that of normal cycles, indicating that the P waves of the paroxysm are ectopic.

The patient was not seen for a year, during which time he was in good health. Two days before this visit, for no apparent cause (except a slight increase in cigaret smoking and in the chronic throat trouble), he observed that his pulse rate was 120, and on getting up suddenly, noticed that he would "feel his heart." Electrocardiograms again showed a long P-R interval (0.32 second), with excessive increase in the heart rate after exercise, and fusion of the P and T waves. This persisted for at least a week; but three weeks later, after the cigaret smoking had been stopped and the throat condition had improved, the P-R interval had again become normal (0.18 second). Since then a year has elapsed and the patient has continued in good health, without any cardiac symptoms.

DISCUSSION

A young, neurotic, male adult, with subjective cardiac symptoms only, was observed on different occasions to have an unusually long P-R interval and a tendency to the auricular (or possibly a sinus) form of paroxysmal tachycardia. This latter occurred at least twice spontaneously, and could be produced at will by exercise or with atropin. It occurred independently of the state of conductivity of the A-V system. For no apparent adequate cause, the P-R interval had been observed twice (an interval of over a year elapsing) to be more than 0.3 second. Once this followed a period of hard study and worry, and once an increase in cigaret smoking in the presence of a chronically inflamed throat. On both occasions the P-R interval returned to normal within a few weeks of the cessation of these conditions, and yet it would be presumptuous to assume that they had a causal relationship.

GENERAL SUMMARY

1. Four different types of transient heart block are described, analyzed and discussed:

(*a*) Transient partial A-V block of myocardial origin, occurring during an exacerbation of acute rheumatic carditis, varying with the degree of arthritis, yet responding to atropin.

(*b*) Transient complete A-V block, brought on by digitalis, and temporarily reducible by atropin to a 2:1 rhythm.

(*c*) The development of defective conductivity in the right branch

of His' bundle in an old man suffering with arteriosclerosis, chronic myocarditis and anginoid symptoms.

(*d*) Transient periods of prolongation of the P-R interval (to more than 0.3 second) without adequate cause in a healthy young adult male. He is also subject to paroxysmal tachycardia of auricular (or sinus) origin, which occurs independently of and does not affect the state of the conductive system.

THE CARBON DIOXID CONTENT OF BLOOD AND OF ALVEOLAR AIR IN OBSTRUCTED EXPIRATION *

E. D. FRIEDMAN, AND H. C. JACKSON
NEW YORK

In asthma the following clinical observations have been made:

1. Low pulse pressure in those cases uncomplicated by arteriosclerosis, probably due to diminished systolic volume.

2. Loud pulmonic second sound pointing towards increased resistance in the lesser circulation.

3. Polycythemia, possibly a teleologic phenomenon designed to compensate for a lessened minute volume output from the left ventricle.

4. Enlarged veins in the neck and cyanosis suggesting a certain amount of general venous stasis.

These clinical facts led us to suspect that circulatory disturbances might account in large part for the conditions associated with obstructed expiration. On account of the lack of adequate clinical material, we decided to study this subject in the experimental animal. Dogs were used.

TECHNIC

The animals received a preliminary injection of 0.16 c.c. of a 2 per cent. solution of morphin per kilogram of body weight. Full anesthesia was produced by the administration through a stomach tube of a saturated solution of chlorbutanol (chloretone) (15 c.c. per kilogram of body weight.)

Tracheotomy was performed. A T-tube was inserted into the trachea and it was so arranged that there was no increase in dead space.[1] As soon as an even anesthesia was obtained, the expired air was collected in a Dreser tube and the minute volume was determined. The carbon dioxid in the blood was determined by means of the Barcroft-Haldane[2] method, that in the alveolar air by Henderson's[3] method. Samples of air were obtained by forcible compression of the thorax at the height of inspiration. A careful series of controls indicated that under the conditions of the experiment, with unobstructed expiration, the CO_2 content of the blood and the alveolar air varied with the minute volume, thus corroborating the work of Haldane and Priestley.[4] Anesthesia for varying lengths of time produced effects varying only with the ventilation.

---

* Submitted for publication Dec. 1, 1916.

* From the Laboratory of Physiology, University and Bellevue Hospital Medical College.

* This work was done during tenure of the C. A. Herter Fellowship in Research Medicine.

1. After our manuscript had been completed, we noted the work of Henderson, Chillingworth and Whitney and that of J. S. Haldane (Am. Jour. Physiol., 1915, **38,** 1) on the variations in dead space. These changes, however, take place only with greatly increased ventilation and do not affect our experiments.

2. Barcroft and Haldane: Jour. Physiol., 1902, **28,** 232.

3. Henderson: Am. Jour. Physiol., 1911-1912, **29,** 441.

4. Haldane and Priestley: Jour. Physiol., 1904-1905, **32,** 225.

In another series, a one-way valve was attached to the vertical end of the T-tube, and by means of a screw, varying degrees of obstruction to expiration were produced. This was our method of simulating the asthmatic attack. The anatomic findings show that we have been successful, especially with regard to the morphologic picture.[5] The obstruction lasted for varying lengths of time. Control determinations were always made before the valve was inserted,

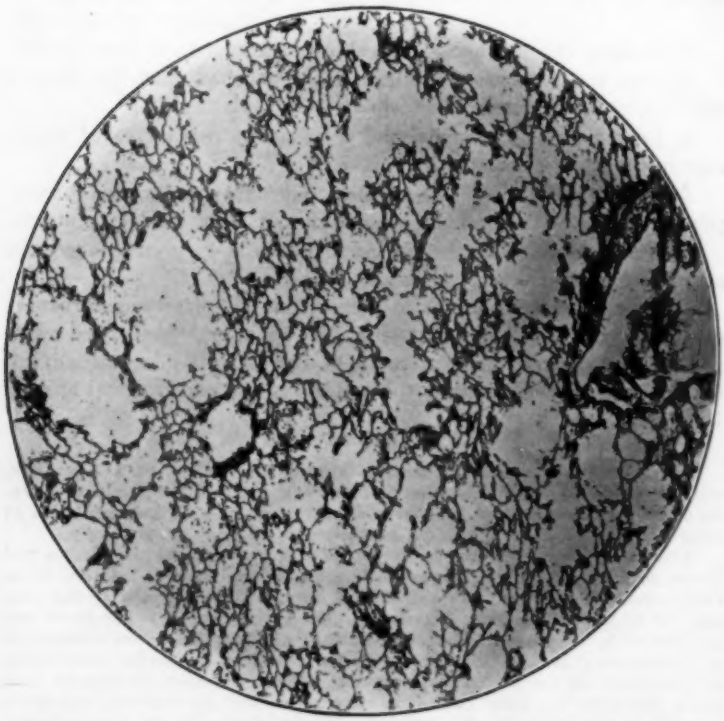


Fig. 1.—Section of lung from valve dog which shows dilated infundibula and ruptured alveoli. Note the extremely thin walls of the alveoli and the ruptured ends projecting into the lumen of the infundibulum. There is no area where normal lung structure could be demonstrated.

5. A pathologic study was made of the lungs of our valve dogs by Dr. Alexander Fraser of the Department of Pathology of University and Bellevue Hospital Medical College, to whom we here express our sincere thanks. He found the macroscopic and microscopic evidences of emphysema with the exception of increase in connective tissue. There were also areas resembling infarctions, probably due to rhexis as a result of the increased resistance in the pulmonary circuit. One of Hoover's patients also coughed up, during an asthmatic attack, a frothy, blood-stained sputum, the source of which might have been one of these areas mentioned by Dr. Fraser. It is of interest to add that Stahelin also noted the occurrence of hemoptysis in some cases.

or before expiration was obstructed by screwing down the valve. A marked increase in the CO_2 content of the blood and the alveolar air occurred especially where increased ventilation had not occurred. In most instances this attempt at compensation showed itself by increased ventilation due to the sensitiveness of the respiratory center to slight rises in the CO_2 pressure in the alveolar air. (Haldane and Priestley.[5]) Usually, however, this attempt at compensation was inadequate, because "there seems to be an optimum of respiratory volume beyond which the effectiveness of ventilation is not proportional to the increase in exchange." (Hoover.[6])

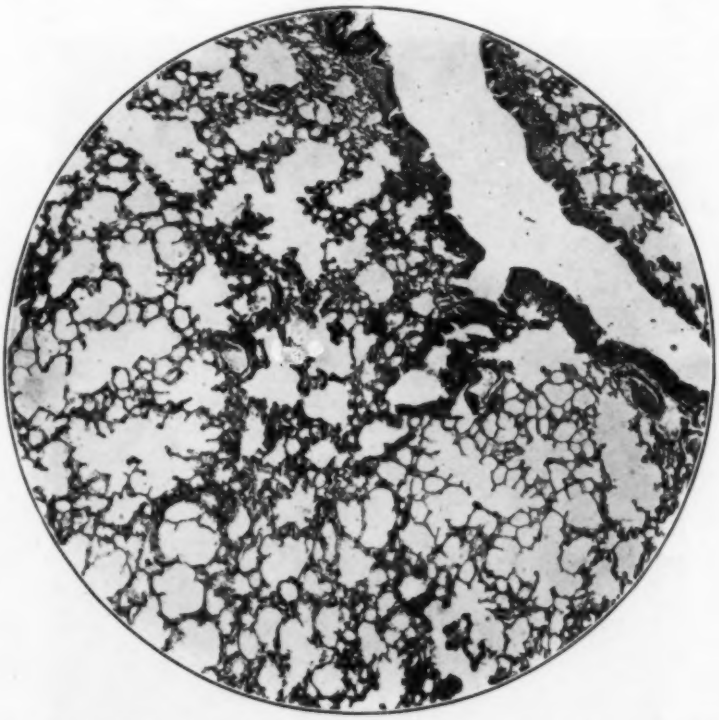


Fig. 2.—Section of lung from normal dog which shows a well distended bit of lung which did not show signs of emphysema macroscopically. The infundibula are fully distended, but the normal relationship between infundibula and alveoli is preserved. The dark areas represent round-cell infiltrations and red cells.

As soon as the obstruction was introduced, the type of respiration changed. Expiration became prolonged, the rate slowed, and the abdominal wall muscles also aided in the attempt to force air out. It seemed possible that increased muscular work might be a factor tending to raise the CO_2 content of the

6. Hoover: The Archives Int. Med., 1913, **11**, 52.

TABLE 1.—Control Experiments

Experiment	Minute Volume	Blood CO_2 Volume, per Cent.	Alveolar Air CO_2 Volume per Cent.	Duration of Experiment, Hours
1 Begin	1,800	52.86	5.34	6
End	2,000	55.53	5.14	
2 Begin	1,500	50.59	5.76	7
End	900	61.18	6.11	
3 Begin	2,700	48.11	5.62	6
End	1,500	80.21	8.53	
4 Begin	2,250	62.10	5.11	6
End	4,400	48.58	4.53	
5 Begin	1,120	60.41	5.28	8
End	1,710	45.74	5.01	
6 Begin	2,570	48.44	7.15	6
End	1,540	64.61	8.28	
7 Begin	1,400	60.22	7.33	6
End	720	69.20	8.19	
8 Begin	2,700	48.46	5.96	6
End	1,500	51.02	6.05	

TABLE 2.—Valve Experiments

Experiment	Minute Volume	Blood CO_2 Volume, per Cent.	Alveolar Air CO_2 Volume per Cent.	Duration of Experiment, Hours
9 Begin	1,560	52.72	5.66	3
End	2,160	61.82	6.88	
10 Begin	1,620	50.80	4.92	8
End	3,625	69.86	5.43	
11 Begin	1,200	35.20	4.01	6
End	2,400	47.80	4.37	
12 Begin	1,800	44.74	5.12	8
End	3,000	64.20	6.35	
13 Begin	1,500	50.68	6.07	6
End	1,000	81.40	9.22	
14 Begin	1,200	44.52	4.64	6
End	1,980	59.43	6.30	

blood.[7] A series of controls was carried out with strychninized dogs. The animals received 2 c.c. of a 1 to 1,000 strychnin solution, hypodermatically, in divided doses, at five minute intervals until a convulsive response was produced by tapping on the nose. These results agreed with those of our control animals, in which the CO_2 in the blood and in the alveolar air varied according to the ventilation.

7. It is of interest in this connection to note the work of Wilson, Stearns and Thurlow (Jour. Biol. Chem., 1915, **23,** 89) who found that tetany following parathyroidectomy tends to lessen the alkalinity and to lower the CO_2 tension of the blood. Our experiments with strychninized animals tend to confirm these results.

TABLE 3.—Strychnin Experiments

Experiment	Minute Volume	Blood CO_2 Volume, per Cent.	Alveolar Air CO_2 Volume per Cent.	Duration of Experiment, Hours
15 Begin	1,080	58.44	7.31	4
End	1,440	44.51	6.66	
16 Begin	1,800	51.66	5.89	4
End	2,100	52.35	5.95	

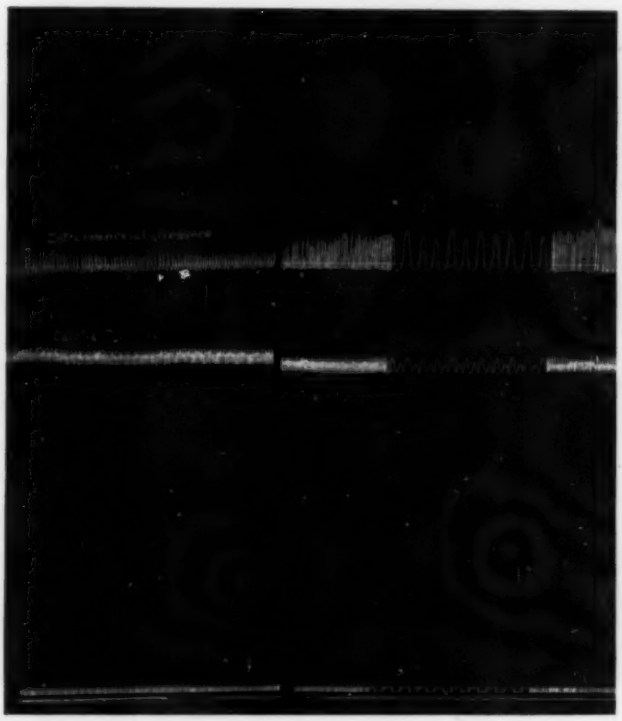


Fig. 3.—Period of beginning obstruction. Note the ratio between the duration of positive and negative intrabronchial pressure. Ratio, negative 1: positive 1.

To get some insight as to events occurring in the circulatory system, carotid pressure observations were made simultaneously with the determination of the intrabronchial pressure.

From a study of the tracings we can conclude that there is at the beginning of expiration a preliminary squeezing out of blood from the pulmonary capillaries and veins into the left heart. This increases the

systolic output from the left ventricle and the carotid pressure rises for a few seconds. After a few beats, however, there is a fall in blood pressure, due to the fact that the intrabronchial pressure exceeds the capillary pressure and interferes with the flow through the compressed capillaries, thus diminishing the return of blood to the left auricle. Suddenly, at the beginning of inspiration, when the intrabronchial pressure falls, the drop in systolic pressure which began toward the

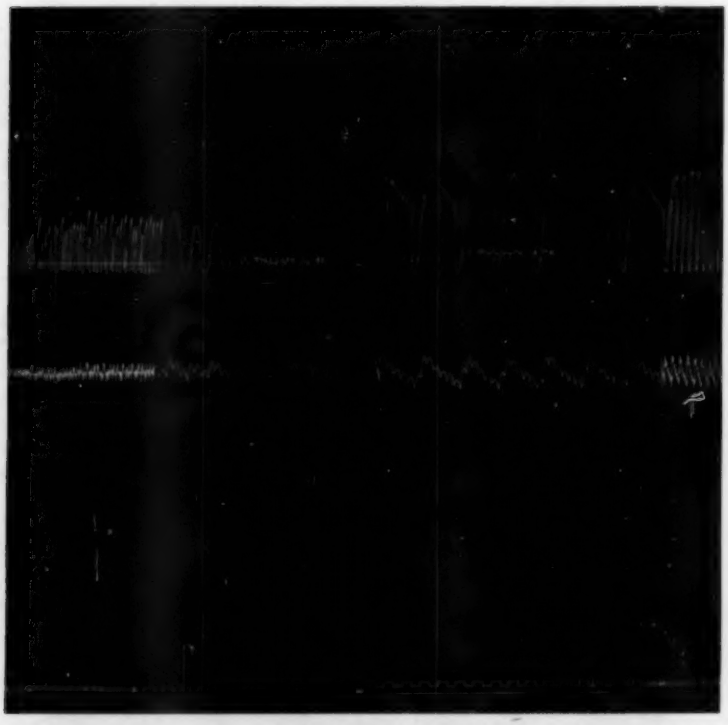


Fig. 4.—Period of increasing obstruction. Ratio of negative pressure to positive pressure. Tracing on left, negative 3: positive 5; tracing on right, negative 1: positive 6.

end of expiration is still further increased. The depleted pulmonary capillaries take up the blood from the right ventricle, and thereby lessen the flow to the left heart. There probably is a shutting off of free flow from the superior vena cava, but due to the rise in the intra-abdominal pressure, the inferior vena cava empties itself into the right heart and thus assures a definite supply of blood to the right heart.

The tracings indicate a diminution of systolic output with rising intrabronchial pressure, and a change in the time relationship between inspiration and expiration. Whereas the normal ratio of inspiration to expiration is 5:4, in our animals it approximated 1:4. On the whole, the tracings point out clearly that there is a distinct interference with

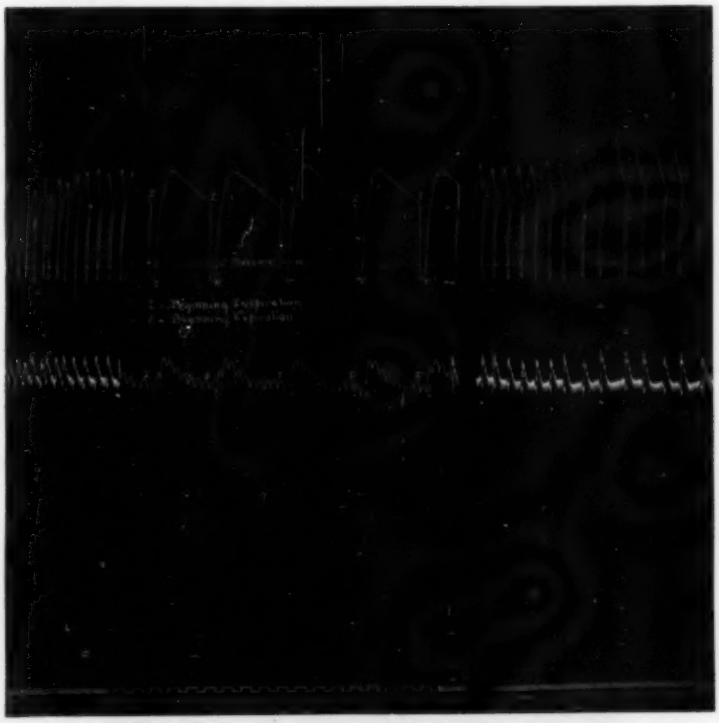


Fig. 5.—Period of increasing obstruction. Ratio of negative pressure to positive pressure. Negative 1: positive 7.

blood flow through the lungs, and therefore with proper aeration, Gerhardt,[8] Minkowski,[9] Tendeloo,[10] Stewart,[11] Romanoff,[12] Cloetta[13] and Bruns[14] are agreed that even slight rises in the intrabronchial

8. Gerhardt: Ztschr. f. klin. Med., 1904, **55,** 195.
9. Minkowski: Therap. d. Gegenw., 1912, **53,** New Series, **14,** 1.
10. Tendeloo: Ergebn. d. inn. Med. u. Kinderh., 1910, **6,** 1.
11. Stewart: Jour. Physiol., 1894, No. 15, p. 31.
12. Romanoff: Arch. f. exper. Path. u. Pharmakol., 1910-1911, **64,** 183.
13. Cloetta: Arch. f. exper. Path. u. Pharmakol., 1911, **66,** 409.
14. Bruns: Deutsch. Arch. f. klin. Med., 1912, **108,** 469.

pressure cause considerable obstruction to blood flow through the lungs, the pressure in the pulmonary capillaries not being much above 0.

Hoover[15] has attempted to explain the insufficient aeration of the blood in asthmatics on a respiratory basis. He found that the CO_2 content of the alveolar air rose in the asthmatic attack, especially where the patient had already suffered from emphysema. He first thought that an increase in the dead space, with impaired alveolar ventilation,

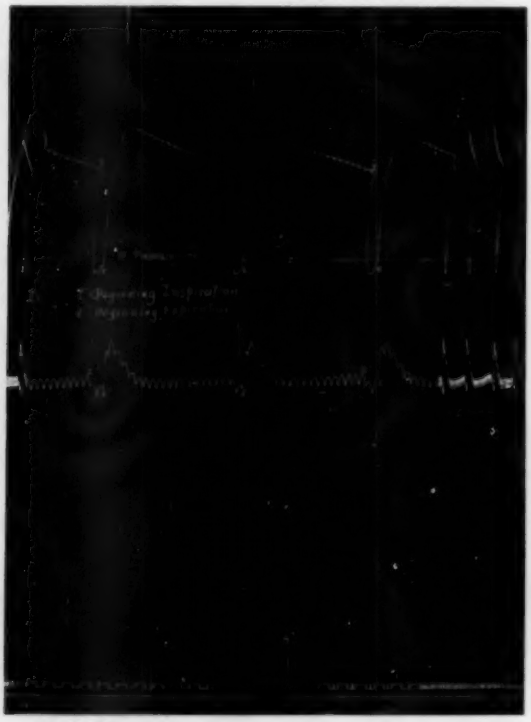


Fig. 6.—Period of maximum obstruction. Intrabronchial pressure, 22 to 25 mm. mercury. Ratio of negative pressure to positive pressure, negative 1; positive 15.

was the cause of this rise. Later observations showed that there was no appreciable increase in the dead space in these cases. In fact, he says that "the dead space is no larger in these cases than in normal persons." The cause of the disturbance in aeration could not be circulatory, for he says "to produce cyanosis by impairment in circulation,

15. Hoover: THE ARCHIVES INT. MED., 1915, **15**, 1 and 501.

the evidence of venous stasis must be very great." Yet we all know that most emphysematous patients show rather well marked cyanosis without any evidence of hepatic congestion, edema, etc. He concluded from his studies that "the real difficulty of ventilation in asthma lies in a distention of the infundibula, and this fails to permit an equal diffusion of CO_2 throughout the alveolar air," an explanation, which does not seem plausible, especially when one recalls the relatively large diffusion coefficient for CO_2.

Fig. 7.—Note decreasing systolic volume as intrabronchial pressure rose. Upper tracing, intrabronchial pressure; lower tracing, carotid pressure; a, beginning of expiration, b, beginning of inspiration.

In view of all these facts, we are inclined to believe that the circulatory factor, contrary to Hoover, is the important one. The cough in asthmatics, which, according to Gerhardt, can raise the intrabronchial pressure to 57 mm. of mercury, and according to Aron to 90 mm. of mercury, would distinctly embarrass the lesser circulation as outlined

in the foregoing, and the voluntary attempts to aid expiration would accentuate the condition. An asthmatic attack in an emphysematous individual would still further distend an already overexpanded lung. Hoover found especially high readings for blood and alveolar air CO_2 in such cases. If we take into account the time relationship between inspiration and expiration, we find that in our animals expiration lasted about four times as long as inspiration. There is, therefore, during four-fifths of the respiratory cycle, the long drawn-out expiration, a positive intrabronchial pressure as a result of which resistance to the flow of blood through the pulmonary capillaries is great. During this phase there is a little opportunity for gaseous exchange. Then there follows only a short inspiration, during which the CO_2 is released as the blood is taken up by the depleted pulmonary sponge. Stahelin[16] remarks that during the Valsalva test, straining with a closed glottis, one sees during Roentgen-ray examination the heart decrease in size and the carotid pressure fall, an evidence of the fact that due to the rise in intrathoracic pressure, little blood can enter the heart, and it therefore pumps itself out. This is but an extreme degree of the mechanism we have described. So too, we are all familiar with the cyanosis which occurs during the pertussis spasm, the rise in intrathoracic pressure causing venous stasis and interfering with free flow to the heart. The absence of a permanent fall in blood pressure in our animals may be explained by a compensatory vasomotor contraction of the systemic arterioles and the emptying of the inferior vena cava by the increased intra-abdominal pressure.

SUMMARY

The high CO_2 content of the alveolar air in asthma and obstructed expiration in general is due to a circulatory cause. The rise in intrabronchial pressure during the long expiration interferes with the free flow of blood through the pulmonary capillaries and causes a damming back of the blood on the venous side. There is a consequent accumulation of CO_2 in the blood with the liberation of CO_2 into the alveolar air, chiefly during the short inspiratory phase of asthmatic breathing.

16. Stahelin: Jahresk. f. ärztl. Fortbild., München., 1913. Part 2, p. 50.

A STUDY OF BLOOD SUGAR

A COMPARISON OF THE TOLERANCE FOR GLUCOSE IN DIABETIC AND NORMAL SUBJECTS *

ROLAND CUMMINGS, M.D., AND GEORGE PINESS, M.D.
LOS ANGELES

The method used in these experiments of estimating the blood sugar was a modification of that of Lewis and Benedict,[1] and very similar to that of Epstein.[2]

TECHNIC

Eight-tenths cubic centimeter of a 0.2 per cent. solution of sodium fluorid is placed in a small test tube. To this is added 0.2 c.c. of blood obtained with a capillary pipet from a finger prick; 1.5 c.c. of a saturated picric acid solution is then added drop by drop and well shaken.

If the picric acid is not added at once glycolysis takes place so the percentage is too low. We had to throw out one series of experiments before we discovered that this was the difficulty.

The mixture is then placed in a centrifuge tube, and centrifuged for two minutes. One cubic centimeter of the filtrate is then placed in a small Jena test tube to which is added 0.5 c.c. of a 10 per cent. sodium carbonate solution, a glass bead, and a drop of kerosene. This is slowly boiled over a microburner until but a few drops remain. Five to 10 drops of distilled water are added and the solution is heated for a moment; then it is poured into a Sahli hemoglobinometer tube and tested against a colorimeter tube of the same diameter containing a standard picramic acid solution so arranged that each line on the tube equals $\frac{1}{1000}$ of 1 per cent. of sugar, or 1 mg. to 100 c.c. of blood.

McLeod and Pierce,[3] after working with the various methods, concluded that the technic of Lewis and Benedict was the best one they had used. The technic as we followed it is almost identical with the original, with the exception that we used but one-tenth as much blood and one-tenth of the various solutions used in the original. Hence our percentage of error is naturally larger, yet we found by paying careful attention to detail and by having all tubes cleaned with care, our percentage of error was no greater than that of usual clinical laboratory tests.

We frequently checked our instrument up with weighed glucose solutions. Glucose solutions, 0.05 and 1 per cent., were carefully prepared and were tested just as though they were blood.

Table 1 is one of a number of similar tables we made from time to time.

---

* Submitted for publication Oct. 25, 1916.

1. Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, **20,** 61.
2. Epstein, A. A.: Jour. Am. Med. Assn., 1914, **63,** 1667.
3. Pierce, R. G.: Jour. Biol. Chem., 1915, **22,** 525.

TABLE 1.—Solution Containing 0.05 Per Cent. or 50 Mg. of Glucose to 100 C.c.

Test No.	Mg. Sugar Per 100 C.c. Solution
1	48
2	53
3	49
4	49
5	50
6	53

TABLE 2.—Solution Containing 0.1 Per Cent. or 100 Mg. Glucose Per 100 C.c.

Test No.	Mg. Sugar Per 100 C.c. Solution
1	95
2	100
3	100
4	105
5	98
6	102

NORMAL BLOOD SUGAR

When reviewing the literature one is struck with the wide variations given by various authors as normal amounts of sugar in the blood (Table 3). None of these investigators examined more than twenty subjects, however.

TABLE 3.—Amount of Blood Sugar Found by Various Authors

Author and Method	Blood Sugar, Per Cent.
Naunyn[4] with Abeles'	0.07 to 0.1
Klemperer[5]	0.06 to 0.11
Hollinger[6] with Knapp's	0.07 to 0.1
Bang[7] with Bang's Micro-	0.1 to 0.11
Frank[8] with Bertrand's	0.06 to 0.11
Purjez[9] with Bertrand's	0.045 to 0.087
Kowarsky[10] with Kowarsky's	0.05 to 0.11
Strause[11] with Kowarsky's	0.04 to 0.088
Hopkins[12] with Bang's Micro-	0.065 to 0.1

Table 4 is composed of results obtained by examination of the blood from one hundred convalescent male patients at the Los Angeles County Hospital who were chosen because of apparently normal digestive systems, and who were about to be discharged from the hospital. The specimens of blood were all taken before breakfast, or

4. Naunyn: Diabetes Mellitus, 1906.
5. Klemperer: Quoted by Bang, see Note 7.
6. Hollinger, A.: Deutsch. Arch. f. klin. Med., 1909, **92,** 217.
7. Bang, I.: Der Blutzucker, 1913, J. F. Bergman, Wiesbaden.
8. Frank, E.: Ztschr. f. physiol. Chem., 1910, **70,** 129.
9. Purjez, B.: Wien. klin. Wchnschr., 1913, **26,** 1420.
10. Kowarsky, A.: Deutsch. med. Wchnschr., 1913, **39,** 1635.
11. Strause, S.: Bull. Johns Hopkins Hosp., 1915, **26,** 292.
12. Hopkins, A. H.: Am. Jour. Med. Sc., 1915, **149,** 254.

at least three hours after meals, Hopkins having shown that the blood sugar had fallen to the same level three hours after meals as the level in a fasting or empty stomach.

TABLE 4.—Results of Blood Sugar Tests in 100 Male Convalescents

No.	Age	Per Cent. Sugar	Mg. Sugar in 100 C.c. Blood
1	49	0.044	44
2	20	0.044	44
3	36	0.049	49
4	59	0.049	49
5	28	0.049	49
6	48	0.053	53
7	28	0.053	53
8	23	0.055	55
9	23	0.055	55
10	55	0.055	55
11	..	0.055	55
12	44	0.056	56
13	39	0.057	57
14	49	0.057	57
15	31	0.057	57
16	24	0.057	57
17	35	0.057	57
18	23	0.058	58
19	43	0.058	58
20	45	0.058	58
21	49	0.058	58
22	69	0.058	58
23	65	0.060	60
24	61	0.060	60
25	..	0.060	60
26	65	0.061	61
27	66	0.061	61
28	66	0.061	61
29	52	0.061	61
30	50	0.061	61
31	42	0.061	61
32	35	0.061	61
33	44	0.061	61
34	51	0.061	61
35	40	0.063	63
36	60	0.063	63
37	59	0.064	64
38	29	0.064	64
39	52	0.064	64
40	35	0.064	64
41	20	0.066	66
42	40	0.066	66
43	62	0.066	66
44	34	0.066	66
45	15	0.066	66
46	55	0.067	67
47	58	0.068	68
48	65	0.068	68
49	33	0.068	68
50	30	0.070	70
51	24	0.071	71
52	..	0.071	71
53	25	0.071	71
54	43	0.071	71
55	28	0.071	71
56	43	0.071	71

TABLE 4—*Continued*

No.	Age	Per Cent. Sugar	Mg. Sugar in 100 C.c. Blood
57	66	0.071	71
58	20	0.071	71
59	27	0.071	71
60	..	0.073	73
61	40	0.073	73
62	30	0.073	73
63	21	0.073	73
64	41	0.073	73
65	60	0.073	73
66	35	0.074	74
67	13	0.074	74
68	22	0.074	74
69	26	0.075	75
70	60	0.075	75
71	..	0.077	77
72	45	0.077	77
73	36	0.077	77
74	26	0.077	77
75	25	0.077	77
76	55	0.077	77
77	18	0.078	78
78	..	0.078	78
79	..	0.079	79
80	12	0.079	79
81	..	0.079	79
82	41	0.080	80
83	71	0.081	81
84	73	0.082	82
85	24	0.082	82
86	42	0.082	82
87	18	0.082	82
88	42	0.082	82
89	65	0.084	84
90	34	0.087	87
91	62	0.088	88
92	36	0.090	90
93	..	0.090	90
94	65	0.090	90
95	52	0.092	92
96	52	0.100	100
97	36	0.100	100
98	49	0.110	110
99	41	0.115	115
100	42	0.120	120

In Table 4 it will be noted that the glucose varies from 44 to 120 mg. to 100 c.c. of blood. Outside of the normal variation of the amount of sugar in the blood, the two main factors producing the wide difference are errors in technic and disobedience of orders about food and drink. The maximum, minimum, and average compare very closely, however, with the figures of the authors quoted.

BLOOD SUGAR IN DIABETES

Table 5 gives data of eleven diabetics taken under the same conditions as the one hundred normals (Table 4).

TABLE 5.—Blood Sugar in Eleven Diabetics

No.	Age	Per Cent. Sugar	Mg. Sugar in 100 C.c. Blood
1	..	0.044	44
2	..	0.060	60
3	..	0.082	82
4	62	0.082	82
5	..	0.104	104
6	60	0.110	110
7	46	0.123	123
8	60	0.126	126
9	62	0.132	132
10	62	0.143	143
11	..	0.143	143

The eleven subjects in Table 5 all had outspoken diabetes, yet the first six, on a single examination of the blood, would have to be classed within the group of normals. It is evident, then, that merely the estimation of the amount of glucose in the blood may give us no correct information of the ability of the patient to handle sugars.

TOLERANCE FOR SUGAR IN NORMALS

Baudouin[13] gave to six normal persons 100 gm. of glucose and examined the blood before, and also one hour and two hours after, taking the sugar. He found a distinct rise of blood sugar one hour after; but two hours after, it had dropped practically to normal.

Frank[6] found like results in eight subjects examined.

Tachau[14] found in nineteen subjects examined, no distinct rise one hour following 100 gm. of glucose.

Bang[7] found a distinct rise following 100 gm. of glucose, but no greater rise when 150 gm. were given.

Bing and Jacobson[15] found in neurasthenia a rise one hour after 100 gm. of glucose, dropping to normal, or nearly normal, at the end of the second hour.

In diabetic patients they found a greater rise than in normal subjects, but observed no definite relation between the blood sugar content and the glycosuria.

Bergmark[16] observed both adults and children, examining the blood before, one hour, two hours, and, in some, three hours after giving 10 to 100 gm. of glucose, lactose, saccharose and maltose.

The maximum rise after these various amounts was from one to one and one-half hours, with a fall to normal in two to three hours. It made little difference which variety of sugar was used.

13. Baudouin: Thèse de Paris, 1908.
14. Tachau: Deutsch. Arch. f. klin. Med., 1911, **102,** 297.
15. Bing, H. J., and Jacobsen, B.: Deutsch. Arch. f. klin. Med., 1914, **113,** 571.
16. Bergmark: Jahrb. f. Kinderh., 1914, **80,** 373.

TABLE 6.—METABOLISM OF SUGAR IN APPARENTLY NORMAL PERSONS

No.	Age	Fasting; Mg. Sugar per 100 C.c. of Blood	First Hour; Mg. Sugar per 100 C.c. of Blood	Second Hour; Mg. Sugar per 100 C.c. of Blood
1	40	37	38	62
2	49	44	73	77
3	..	46	63	56
4	..	49	63	63
5	28	49	101	68
6	..	50	114	97
7	28	52	71	68
8	48	52	71	68
9	..	55	92	71
10	..	55	89	95
11	23	55	93	88
12	55	55	123	96
13	..	57	85	71
14	24	57	89	115
15	35	57	84	55
16	..	58	73	67
17	44	58	121	88
18	65	58	82	66
19	..	60	74	66
20	..	60	114	119
21	50	61	93	70
22	52	61	127	121
23	66	61	129	111
24	..	62	93	88
25	40	62	118	107
26	..	63	83	68
27	59	63	114	94
28	35	64	119	99
29	..	66	93	77
30	..	66	121	121
31	58	68	137	121
32	43	71	71	55
33	28	71	83	71
34	24	71	104	99
35	..	71	204	123
36	25	71	102	93
37	27	71	102	88
38	60	72	119	110
39	41	72	117	148
40	20	72	123	115
41	56	74	108	99
42	18	77	79	72
43	45	77	125	110
44	56	77	88	80
45	26	77	104	71
46	25	77	127	115
47	55	77	91	73
48	..	77	91	91
49	..	79	70	79
50	42	82	110	66
51	18	82	110	66
52	..	84	115	111
53	34	87	123	110
54	..	87	78	85
55	..	89	110	81
56	..	93	107	99
57	..	90	88	77
58	..	110	159	110
Average		68	101	88

In order to ascertain the ability of a normal person to absorb and metabolize sugar, we gave 100 gm. of glucose or cane sugar to each of fifty-eight apparently normal persons. Table 6 gives their ages and the number of milligrams of sugar found in 100 c.c. of blood on a fasting stomach, and one hour and two hours after administering sugar.

In Table 6, except in Cases 1, 2, 14, 20, 39, 49 and 54, the sugar is higher at the end of the first hour than at the end of the second. The average is quite typical of the great majority. There is about a 50 per cent. rise during the first hour, with a drop of about one-half this during the second hour. These results correspond quite closely to the observations of Baudouin, Frank, and Bergmark.

TOLERANCE FOR SUGAR IN DIABETICS

The series of fourteen outspoken diabetics (Table 7) shows quite different results.

TABLE 7.—TOLERANCE FOR SUGAR SHOWN BY DIABETICS

No.	Age	Fasting; Mg. Sugar per 100 C.c. of Blood	First Hour; Mg. Sugar per 100 C.c. of Blood	Second Hour; Mg. Sugar per 100 C.c. of Blood
1	..	44	99	143
2	..	60	93	137
3	62	82	93	93
4	..	22	99	159
5	..	104	104	143
6	60	110	121	110
7	14	110	150	200
8	52	120	280	340
9	46	123	137	170
10	60	126	159	165
11	56	130	155	190
12	62	132	308	373
13	62	143	176	220
14	..	143	170	209

The technic of testing these diabetics (Table 7) was the same as that used in the normal subjects, yet the curve is quite different. Except in Cases 3 and 6, there is a greater amount of sugar at the end of the second hour than at the end of the first, and in most of the cases the rise is quite marked. In Cases 3 and 6 the patients had been under treatment for some time, and there had developed a distinct increase in their tolerance.

Two subjects were examined who we believe had some time previously had diabetes. The results are distinctly suggestive of a low tolerance.

REPORT OF CASES

Dr. E., aged 30, who four years previously had had a glycosuria, polyuria and a furunculosis which did not yield to any form of treatment until the

patient was placed on a low carbohydrate diet, had been free from glycosuria for many months. His blood during the fasting period contained 65 mg. per 100 c.c. One hour after 100 gm. of glucose was ingested there were 135 mg., and two hours after, it contained 90 mg. Here we have a normal amount of sugar during the fasting period, but after giving sugar, a marked rise, followed

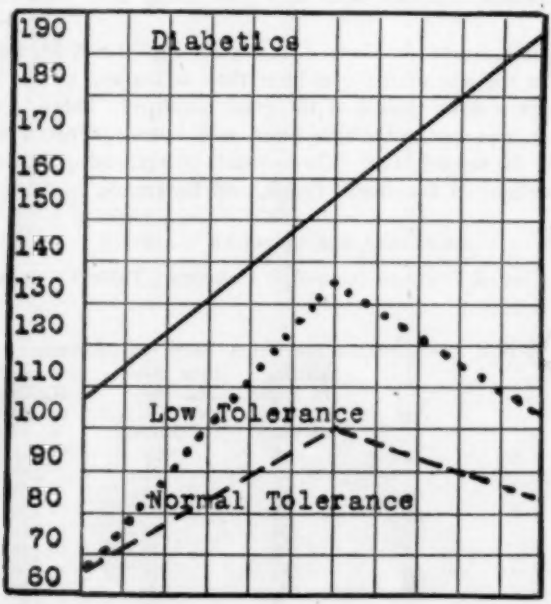


Chart showing variations from the normal in lowered sugar tolerance.

Average	Fasting, Mg.	First Hour, Mg.	Second Hour, Mg.
Normal	68	101	88
Low tolerance.....	65	135	105
Diabetics	108	153	190

in two hours by a drop, which is still 50 per cent. above his fasting level. No glycosuria was present during this test.

Mrs. E., aged 34, who was still under treatment, but whose urine had been sugar-free for some time, had, during the fasting period, 65 mg. of sugar in 100 c.c. of blood; one hour after administering 100 gm. of glucose there were 132 mg., and two hours later the blood still contained 121 mg. This case shows distinctly a low tolerance for sugar. Glycosuria developed during this test.

Taking the average in these three groups of subjects, we constructed the accompanying chart, the curves of which show in a concrete manner the variations from the normal in those cases having a lowered tolerance for sugar.

SUMMARY

1. We have made several hundred estimations of the amount of sugar in the blood by a simple technic which is a modification of Lewis and Benedict's method, and believe it to be reasonably accurate.

2. We measured the amount of sugar in the blood of 100 apparently normal subjects, finding the minimum to be 44 mg., the maximum 120 mg., with the average 70 mg. sugar per 100 c.c. of blood.

3. We estimated the tolerance of fifty-eight normal subjects for sugar, finding the maximum amount of sugar in the blood to be at the end of the first hour following the ingestion of 100 gm. of glucose, with a drop almost to normal at the end of the second hour.

4. We estimated the tolerance for sugar in fourteen cases of outspoken diabetes, finding more sugar in the blood at the end of two hours after the ingestion of 100 gm. of glucose than at the end of one hour, as in the normals.

5. We estimated the tolerance for sugar in two subjects who had apparently had diabetes, finding a marked rise during the first hour, with but a moderate fall during the second hour.

CONCLUSIONS

1. From our observations we conclude that in a real or moderately severe case of diabetes the blood sugar is higher two hours after giving 100 gm. of glucose than it is one hour after.

2. In the milder forms of diabetes the blood sugar will be found normal, but following the administration of 100 gm. of glucose the rise in blood sugar will be greater than normal, and especially will this rise be sustained well into the end of the second hour.

3. In subjects having a low tolerance for sugars, the rise following the ingestion of 100 gm. of glucose will not be so high as in diabetes, yet it is distinctly higher than normal, and the height is well sustained into the end of the second hour.

1240 Merchants National Bank Building.

THE HUMAN AND ANIMAL LIVER AFTER ALCOHOL*

FRANK A. McJUNKIN, M.D.
MILWAUKEE, WIS.

INTRODUCTION

Long before the microscope came to play the important rôle in pathology that it now does, the liver, in common with other large organs, presented changes for gross study. Thus Laennec[1] in his work on auscultation, published in 1829, mentions in a case of ascites the presence of a small liver with coarsely granular surface. Owing to the yellowish color of the organ he applied the term *cirrhose*.

The term cirrhosis has survived, and, like other terms that are not applied to given conditions of definite etiology, it has not always been used in the same way. We do not hesitate to call the condition in which there is a complete loss of liver lobules with the formation of wide bands of connective tissue, a cirrhosis, but if there is a moderate increase of connective tissue about the portal areas and along the interlobular lines, the term sclerosis is likely to be preferred. Many authors, however, speak of the moderate increase of connective tissue that may follow, for instance, a tuberculous process in the liver, as a cirrhosis. At present, perhaps, the commonest usage is to apply cirrhosis to the more extensive grades of sclerotic change in the liver.

Following the observation of Laennec, a large mass of literature accumulated dealing with the etiologic factors that produce or appear to produce liver cirrhoses. For the most part it is difficult to place the credit for our present knowledge of the causative agents. MacCallum[2] and Kretz[3] have pointed out the way in which regeneration of the cells gives rise to large islands of liver cells with complete loss of lobulation; Levaditi and others are responsible for our ability to demonstrate the relationship between the Treponema pallidum in the liver and the sclerotic changes present; while Mallory[4] has shown that a characteristic hyaline (Fig. 1) change is present in the cytoplasm of the liver cells of cirrhosis of a certain type.

---

* Submitted for publication Nov. 6, 1916.

* From the Pathological Laboratory, Boston City Hospital, and the Pathological Department, Marquette University School of Medicine.

1. Laennec, R. T. H.: De L' Auscultation Mediate, 1819, **1**, 368.
2. MacCallum, W. G.: Regenerative Changes in Cirrhosis of the Liver, Jour. Am. Med. Assn., 1904, **43**, 649.
3. Kretz, R.: Ueber Lebercirrhose, Wien. klin. Wchnschr., 1900, **12**, 271.
4. Mallory, F. B.: Bull. Johns Hopkins Hosp., 1911, **22**, 69.

The etiology of those cirrhoses, in which the causative agent is present in the tissue as a morphologic element, was the first to be established, and there is at present, therefore, much greater certainty in regard to the mechanical (carbon and hemosiderin deposits), infectious (colon and possibly other ascending gall-duct infections) and syphilitic varieties than there is concerning the toxic. Leaving out of account the central scleroses produced by certain bacterial toxins and which may be induced by chloroform, the etiology of toxic liver lesions is yet obscure. This applies to the sclerosis following acute yellow atrophy.

Owing to the frequent history of alcoholism, ethyl alcohol was looked on as an active factor in the production of liver cirrhosis shortly after the observations of Laennec. Later, cirrhotic livers were found in infants and youths that had never used alcohol. This confused matters until the mechanical, syphilitic, and infectious varieties were clearly defined. Now, as during the earlier observations, a feature of these cases of unknown etiology is the excessive use of alcohol, especially of distilled liquors.

HUMAN CIRRHOSIS OF UNKNOWN ETIOLOGY

In a series of thirty recent cases of cirrhosis of unknown etiology coming to necropsy from the wards of the Boston City Hospital, the clinical records of twenty-eight make note of alcoholism. On the other hand, the majority of those dying from chronic alcoholism in the alcoholic wards of the hospitals show no abnormal changes in the liver. The excessive use of alcohol does not, therefore, always produce liver lesions in the human, while some workers along this line are willing to say that it never does. Many say that it does so indirectly by causing lesions in the gastro-intestinal tract, with a resulting autointoxication, while others say that alcoholic cirrhosis results from some impurity in the liquors. The most that can be said from the clinical study of human cases is that the majority of those with a cirrhosis not infectious or syphilitic (and not mechanical) use or have used alcohol to excess.

These cases were chosen from necropsies performed at the Boston City Hospital by examining the sections of liver for hyalin-containing cells. This examination excluded cases of sclerosis resulting from an attack of so-called acute yellow atrophy, in which the hyaline degeneration is not present and the lesion is not active and progressive. The microscopic examination makes possible the elimination of mechanical lesions from carbon or other pigment deposits and lesions from the extension of an infectious process up the bile passages, while the microscopic and gross appearance, together with the clinical history and clinical laboratory tests enable one to be quite sure that no cases of syphilis are included. These cases, then, are instances of cirrhosis

of unknown etiology, most of which are more or less alcoholic. The chief interest in the series is that the similarity in the microscopic appearance points to one toxic agent or to toxic substances acting in practically the same way. Thirty cases were taken; of these, Cases 1 to 5 show very little sclerosis, 6 to 9 are in the transition stage, while 10 to 30 are late, with extensive sclerosis. Cases 1 to 10 show each step in the process that ends with the typical "hobnail" liver.

The hyaline network in the affected cells has been accurately described by Mallory. This change is fully as evident as the nuclei of the cells themselves (Fig. 1). It is not present in cirrhosis of known etiology and is lacking in the degenerating cells of other liver affections. An interesting feature of the histologic study of the early cases (1 to 9) is that although the lobules are irregularly involved, the process is more severe toward the central hepatic vein.

To summarize, the thirty cases of this series are not cirrhoses of mechanical, infectious or syphilitic origin in the sense that these terms are used in the foregoing. Although the liver lesion is of toxic origin, it differs from acute yellow atrophy where the lesion is not progressive and where there is no hyaline degeneration of the liver cells, and from the central necrosis and sclerosis that may follow chloroform or bacterial toxins, where the lesion is not progressive and there are no hyaline-containing cells.

REPORT OF CASES

CASE 1.—M. F., woman, aged 28. The patient's sister says "patient has been drinking a good deal of late;" clinical diagnosis, alcoholic neuritis; patient died eleven days after admission to the hospital.

Liver weighs 1,800 gm.; the surface is smooth; microscopically the normal lobulation is present; there is no necrosis and no sclerosis. A few lobules have a single cell with a typical hyaline network. The other cells are normal except for a slight edema of those near the central vein. In all of the following cases there has been a loss and a failure of regeneration of a sufficient number of cells to lead to areas of sclerosis in the lobules or to sclerosis of entire lobules.

CASE 2.—J. W., man, aged 33. During the last few weeks the patient has grown weaker and at his lodging house he was often helped to his room when intoxicated. He was admitted to the hospital in an unconscious condition and died on the day of admission.

Weight of the liver 1,730 gm.; surface is smooth; microscopically, the lobulation is normal. There is a slight sclerosis which differs from the usual central toxic sclerosis (chloroform, streptococcus toxin, etc.) in that it is not confined to the zone about the central hepatic vein, but extends irregularly at one or more points toward the portal tissue and may even reach the periphery of the lobule.

On examining these areas of sclerosis with an oil immersion lens, a majority of the cells are found to have disappeared, not only from the inner ends of groups of trabeculae, but also from the intermediate and outer portions. Some of the liver cells remaining in these trabeculae are normal while others contain hyalin.

CASE 3.—F. W., man, aged 41. The patient came to the hospital with a history of recent hard drinking, developed delirium tremens and died on the seventeenth day after admission.

Weight of the liver 1,975 gm.; surface is smooth. Microscopically the liver is like that in Case 2.

Case 4.—W. G., man, aged 49, had been very alcoholic, and for two weeks had had facial erysipelas; entered the hospital delirious and died on the second day following admission.

Weight of the liver 2,680 gm.; the surface is granular. Microscopically the liver is like the organs in Cases 2 and 3, except that the loss of cells from trabeculae is very diffuse and the number of hyalin-containing cells in every part of the lobule is practically the same.

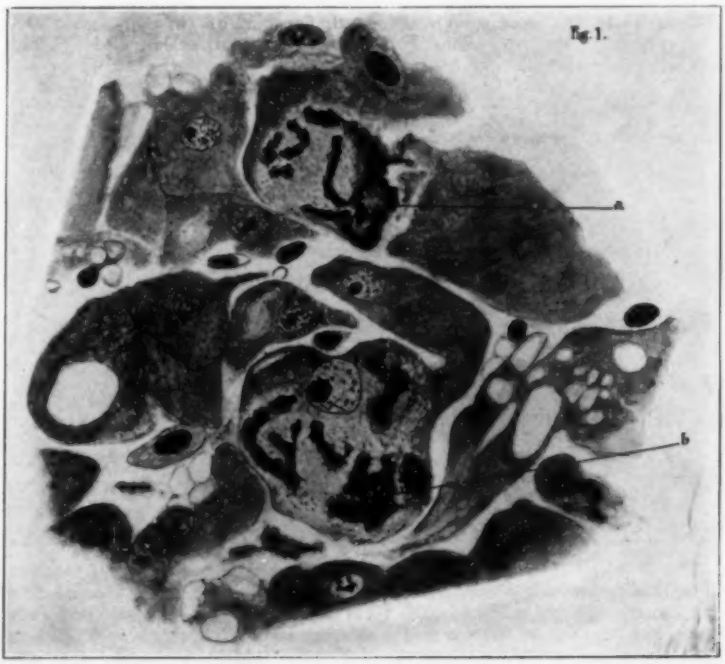


Fig. 1.—High power magnification of the liver from a case of human cirrhosis of unknown etiology (Case 7). *a* and *b* are two cells showing the hyaline degeneration of the cells that characterizes this variety of cirrhosis. *b* shows nucleus intact which is the case in a considerable number of the cells so affected. Such cells are very often invaded by leukocytes, but neither of these cells has been so involved.

Case 5.—G. T., man, aged 35, drank three to four glasses of whisky daily; died on the fifth day after admission.

Weight of the liver 2,560 gm.; surface of the liver is smooth. Microscopically the liver is like the organs in Cases 2 and 3.

Case 6.—M. B., woman, aged 48, drank one pint of whisky per week; also beer. She was intoxicated when admitted to the hospital and died one month from date of admission.

Weight of the liver 2,400 gm.; surface smooth. Here the process is somewhat more extensive. The loss of cells from trabeculae reaches from central veins to portal areas and in many lobules the majority of the cells are gone. Most of the section is made up of sclerosed lobules with small islands of cells about the portal areas. In places an island of normal liver cells lies only on one side of a portal area.

Case 7.—A. W., woman, aged 35, used some alcohol; in bed for one week with vomiting and diarrhea; no jaundice; died six days after admission to the hospital.

Weight of the liver 1,670 gm.; surface is granular. Microscopically the amount of sclerosis is the same as in Case 6.

Case 8.—M. T., woman, aged 55, drank one pint of gin daily; had been a heavy drinker for three years; had jaundice for four weeks; died eighteen days after admission.

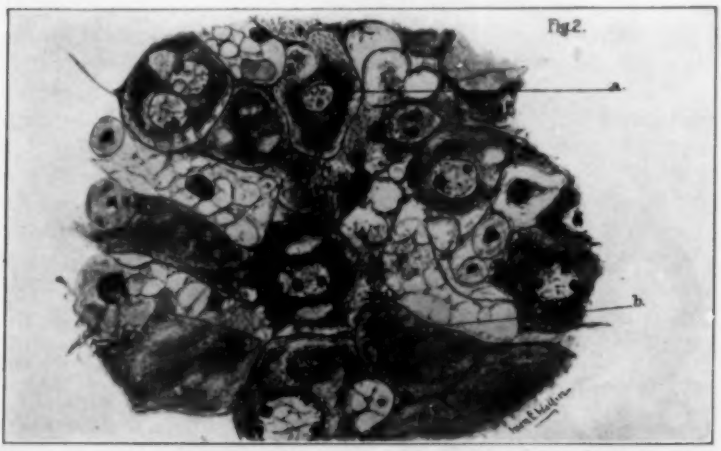


Fig. 2.—High power magnification of the liver from a rabbit that received 4 gm. lead acetate forty-eight hours before being killed. *a* and *b* are two cells that show a fine granulation in the form of a network. Many of these cells become invaded by leukocytes and undergo necrosis. This network gives a black precipitate when treated with an alkaline sulphid, a reaction that differentiates this change from that shown in Figure 1.

Weight of the liver 1,800 gm.; surface is granular. Microscopically this liver is typically in the stage of transition from a sclerosis of lobules to a sclerosis with a loss of lobules and the formation of islands of liver cells. The tendency for these islands of unaffected cells to lie about the portal tissue is shown by the two preceding cases. In some lobules some irregular sclerosis about the central hepatic vein extends to the portal tissue, and in this way circular bands made up of one to several portal tracts are formed. These bands inclose islands of liver cells made up of the parts of one or more lobules next the portal tissue.

Case 9.—L. B., man, aged 58, had never been sick; never used liquor to excess, but drank more during the previous month; jaundiced for one month; gradually weakened and died eighteen days after admission to the hospital.

Weight of the liver 2,750 gm.; surface is granular. Microscopically, sections show beautifully the inclosing of peripheral portions of lobules by bands made up of portal areas connected with the irregular central scleroses.

CASE 10.—B. T., man, aged 50, drank three to four whiskies and four to five beers per day, eight months previous to admission he felt tired in the morning and would take a glass of brandy to stop his vomiting; for two months the abdomen had been enlarging and he had had diarrhea; he was slightly jaundiced on admission and died eight days later.

Weight of the liver 1,220 gm.; surface is granular. Microscopically this liver is made up of islands of liver cells of very irregular shape and size, surrounded by and cut into by rather narrow connective tissue bands. A few of the islands have portal areas at or near their centers.

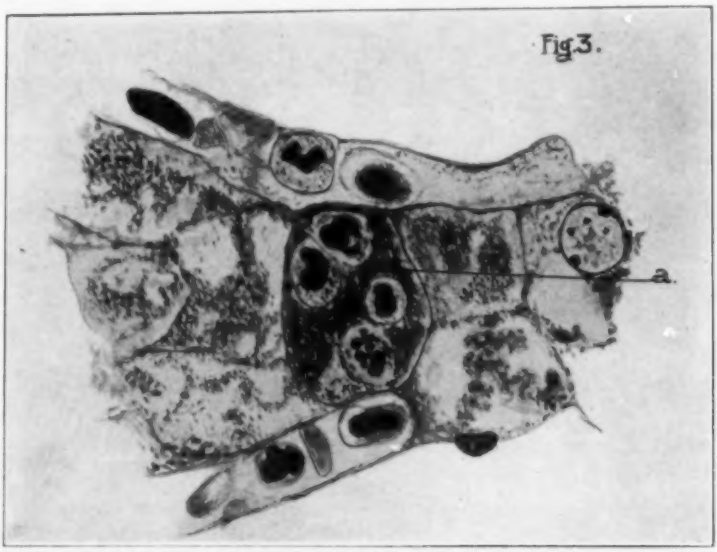


Fig. 3.—High power magnification of the liver from a guinea-pig (No. 46) that had received maximum doses of ethyl alcohol. *a* is a necrotic liver cell lying between two sinusoids. A few such cells represent the greatest damage that can be effected with alcohol. A few cells lost in this way are replaced perfectly.

Reference to the preceding cases offers a clear explanation of the method of formation of these islands. This case differs from the preceding ones in being a more advanced stage of the sclerotic process. That is, the areas of sclerosis involve all lobules to such an extent that all the central hepatic veins and most of the portal areas are included in the fibrous bands.

The islands of normal liver cells are originally made up of a segment of a lobule or the parts of several lobules that abut on portal tissue. That regeneration has taken place in the original islands is

shown by the presence of islands larger than any normal lobules. Mitoses of liver cells may be found in many of these cases, but frequently it is difficult microscopically to find evidence of regeneration.

These islands are subject to hyaline degeneration just as the lobules are in the earlier stages of the process. For this reason, and also owing to the inclusion of small focal necroses in persisting parts of lobules, the islands of liver cells are very diffusely cut into by connective tissue bands that are narrower than those surrounding the

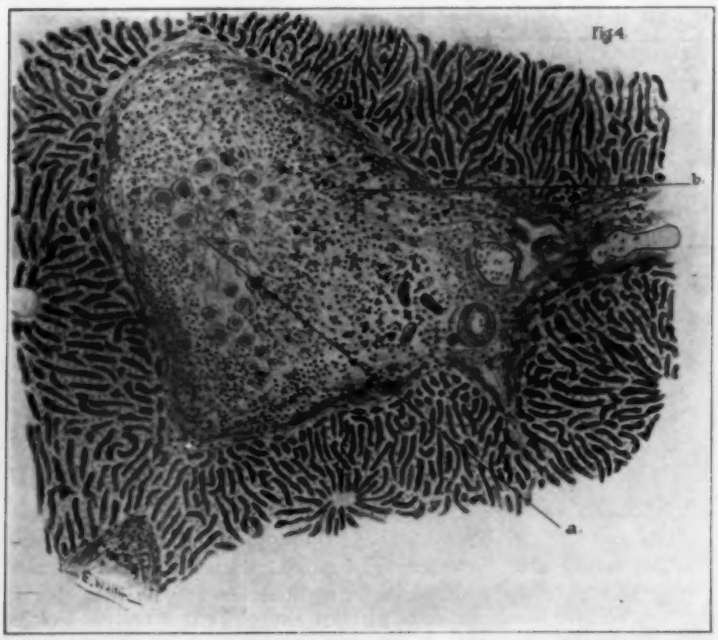


Fig. 4.—Low power magnification of the liver from a rabbit that had never been made the subject of any experiment. This process occurs naturally in rabbits and is found in a large percentage of old animals. The necrosis at *a* and the leukocytic infiltration at *b* are followed by a fibrosis such as was met with in Animal 221. This is the change that has been described by those who claim to have produced a cirrhosis in animals by means of ethyl alcohol.

islands. The narrowness of the bands and this irregular cutting up of the islands is often sufficient to differentiate this variety of cirrhosis from the cirrhosis that follows what is known as acute yellow atrophy.

Case 11.—A. D., woman, aged 46, drank one bottle of beer daily; died thirty days after admission.

Weight of the liver 1,870 gm.; surface is graular. Microscopically it is like the liver in Case 10.

CASE 12.—I. C., woman, aged 50. No history; weight of the liver 1,260 gm.; surface is granular. Microscopically it is like that of Case 10 except that many islands are larger.

CASE 13.—R. M., man, aged 47, drank one pint of whisky and three to four beers daily; for three weeks the abdomen had been increasing in size; some jaundice; died ten days after admission.

Weight of the liver, 1,720 gm.; surface is granular. Microscopically it is like that of Case 10.

CASE 14.—C. D., man, aged 46, drank three to four glasses of whisky per day; for three weeks had been growing weak; admitted to the hospital and died fifteen days later.

Weight of the liver 2,350 gm.; surface is granular. Microscopically the connective tissue bands are narrow and ill-defined, and included in these bands there are a great many cells containing hyalin.

CASE 15.—J. N., man, aged 34, drank much whisky during the previous ten years; had stomach trouble and "dry heaves" for years; delirious for three days before entrance to the hospital, and died ten days later.

Weight of the liver 3,029 gm.; surface is granular. Microscopically it is like that in Case 10, except that the islands are larger.

CASE 16.—A. M., man, aged 50, drank seven to eight beers or whiskies daily; quit work three months previous to admission on account of shortness of breath; died twenty-one days after admission to the hospital.

Weight of the liver 1,750 gm.; surface is granular. Microscopically it is like that of Case 10.

CASE 17.—N. H., woman, aged 38, used alcohol for twenty years; in excess for one year; swelling of the abdomen for five weeks; jaundice present; died twelve days after admission.

Weight of the liver 3,180 gm.; surface is smooth. Microscopically it is like the liver in Case 10, except that the connective tissue bands are very narrow and the islands very large. The liver cells contain a great amount of fat.

CASE 18.—R. M., woman, aged 32, drank a half pint of gin per week; for six weeks especially sick; when admitted had an alcoholic breath; died thirteen days after admission.

Weight of the liver 1,310 gm.; surface is granular. Microscopically it is like that of Case 10.

CASE 19.—E. S., man, aged 37, drank twelve to twenty-five glasses of beer daily and brandy occasionally; for the previous five months he complained of weakness; the previous ten days he was jaundiced and had pain in the epigastrium; died two days after admission.

Weight of the liver 2,900 gm.; surface is granular. Microscopically like the liver in Case 10.

CASE 20.—N. H., woman, aged 38. For the previous nine years the patient used much alcohol; there was jaundice and pain in the back for six months; died one day after admission.

Weight of the liver 2,990 gm.; surface is granular. Microscopically like that of Case 10.

CASE 21.—M. O., woman, aged 60. Admitted unconscious following a fall; no history.

Weight of the liver 1,270 gm.; surface is granular. Microscopically like the liver in Case 10.

CASE 22.—W. B., man, aged 50, drank beer, alcohol, and whisky for years; jaundiced for three months; increasing ascites and edema of the legs.

Weight of the liver 1,555 gm.; surface of the liver is granular. Microscopically like that of Case 10.

CASE 23.—M. F., man, aged 51; alcohol used; admitted in a semiconscious condition with an alcoholic breath; died four days later.

Weight of the liver 1,440 gm.; surface is granular. Microscopically like that of Case 10.

CASE 24.—F. M., man, aged 56, had a "spree" once in two months; vomiting; jaundice; died three days after admission.

Weight of the liver 2,100 gm.; surface is granular. Microscopically like the liver in Case 10 except that the sclerosis is somewhat less advanced (a few lobules may be found).

CASE 25.—G. M., man, aged 29, had used alcohol steadily and to excess for three to four years; well until three months prior to admission when vomiting and swelling of the abdomen began; died thirty-four days after admission.

Weight of the liver 2,425 gm.; surface is granular. Microscopically like that of Case 10.

CASE 26.—E. S., man, came into the hospital complaining of acute rheumatism in the right knee; developed delirium tremens and died twelve days after admission; the clinical diagnosis was alcoholism.

Weight of the liver 2,200 gm.; surface is smooth. Microscopically like the liver in Case 10.

CASE 27.—N. H., woman, aged 41, drank wine every morning; died six days after admission.

Weight of the liver 2,650 gm.; surface is granular. Microscopically like that in Case 10.

CASE 28.—C. L., woman, aged 49. Diarrhea, loss of weight, vomiting and enlargement of the abdomen for one month before entrance. Husband said the patient used alcohol.

Weight of the liver 3,080 gm.; surface is granular. Microscopically like that of Case 10.

CASE 29.—F. P., man, aged 33. Run down for the previous three months; drinking heavily; alcohol in excess for years; since entrance to hospital, delirious.

Weight of the liver 5,335 gm.; surface is granular. Microscopically like the liver in Case 10, except for cells containing a large amount of fat.

CASE 30.—C. T., woman, aged 53. In bed for two months with vomiting; not asked about alcohol; died thirty-five days after admission to the hospital. After the necropsy the husband stated that the patient drank much brandy.

Weight of the liver 1,380 gm.; surface is granular. Microscopically like that of Case 10.

Anatomically, Cases 1 to 9, inclusive, are not ones of frank cirrhosis. They are included in the series because the cells show a characteristic hyaline degeneration. This hyaline change is present in this variety of cirrhosis of unknown etiology, and is found in no other condition, except, rarely, in an alcoholic (Cases 1 to 9) in which the changes point to the active degenerative stage that ends in a cirrhosis. Whatever the toxic substance active in this cirrhosis, the hyaline change appears to be the degenerative lesion.

Accepting these cases as different stages of the process that ends in this variety of cirrhosis, especial interest attaches to the microscopic

changes. In all the earlier cases it is seen that, although the degenerative change strikes quite irregularly throughout the lobule, it makes its first appearance toward the center, and this is the part first lost in the process that extends irregularly and finally destroys the entire normal lobulation.

The descriptions that are available for study deal at length with a fully developed cirrhotic liver, while the degenerative changes that produce this anatomic rearrangement of the liver structure are guessed at by inference. Degeneration and regeneration in the cirrhotic liver are described at length, but little is said in regard to the active lesion that is so severe that the entire normal lobulation is lost. As in other processes that end in sclerosis, the early active stage, summarized in the preceding paragraph and detailed in Cases 1 to 9, inclusive, is the important one to study from the etiologic, anatomic and therapeutic point of view. If the causative factor can be definitely established, it is possible that during this stage the progress of the lesion may be stopped.

The common observation that the livers of those dying from acute and chronic alcoholism show, in the great majority of cases, no change except an abundance of fat in the liver cells, is found true in the study of the necropsies performed at the Boston City Hospital on those dying from alcoholism during fifteen years previous to 1915. There is no question that alcohol as used by chronic alcoholics produces no liver lesion in the great majority of cases.

Another point that indicates that the use of alcohol acts indirectly or not at all, is the length of time intervening between admission of the patients to the hospital and their death (more than one month in four of the thirty cases). Since an active and extensive degenerative change is present in the liver of a person one month after his last dose of alcohol, the degenerative change either persists for this length of time or the alcohol acts indirectly or not at all on the liver cells. The rapidity of necrosis and solution, and the invasion of affected cells by leukocytes, ending in their rapid removal, makes it very unlikely that seriously injured cells persist in that state for so long a time.

THE ANIMAL LIVER AFTER DOSAGE WITH ALCOHOL

With a substance so simple chemically as alcohol, one would expect the action on the lower animals to be similar to that in the human, and numerous attempts have been made to clear up the question of so-called alcoholic cirrhosis by administering alcohol to animals. Out of one list of thirty workers who gave ethyl alcohol to animals, seventeen produced no lesion in the liver, while thirteen produced a cirrhosis. Those that produced a cirrhosis worked with rabbits. Rabbits frequently show an increase in round cells in the periportal tissue and

along the interlobular lines (Fig. 4). In this way islands of liver cells and liver lobules become surrounded by fibroblastic tissue. There seems to be some contention as to whether this process, occurring spontaneously in rabbits, should be called a cirrhosis, but disregarding this technicality, it does correspond to the reproductions and descriptions representing the cirrhosis said to be produced by alcohol in rabbits.

A search through the reports of these investigators is a rather barren one. Those reporting positive results have, as mentioned above, made use of rabbits, and their positive results are based on descriptions that correspond to the natural lesion found in these animals. Although investigators now agree that an extensive necrosis and loss of liver cells leads to the cirrhotic liver as an end result, the majority of the experimental workers have made little or no attempt to demonstrate this active process that leads to the sclerosis. In such a case as this in which all the factors used in the experiments are so accessible, it seems largely a waste of time to go into an extensive critical analysis of the literature.

Since alcohol appeared to be the most obvious factor, it was given persistently to animals until it was found that no lesion, however slight, could be produced. Later, other substances were tried. A total of 300 animals were used in the series of experiments. Of these, 125 were given ethyl alcohol (Table 1).

Alcohol.—The alcohol was given by the stomach, subcutaneously, intraperitoneally, by the rectum, by injection into the common bile duct, and by injection directly into the liver. In the animals receiving the alcohol per os, 80 per cent. alcohol was usually given daily or on alternate days and in doses sufficiently large to render the animal unable to stand. Usually it was given on an empty stomach.

In the liver of no animal is there a necrosis and degeneration of liver cells such as is seen in the human cases. Direct injection into the liver and injection into the common duct gave a focal necrosis of course, but the necrotic cells show no peculiarity. In the other animals a few necrotic cells (Fig. 3), usually less than twenty-five per microscopic lobule, are present, but such small numbers of scattered necrotic cells are found in the livers of animals dying from a variety of causes. Animals that died were subjected to necropsy and the organs fixed within one hour, and usually within ten minutes, after death. This is an absolutely necessary precaution, especially in small animals.

The length of time during which the alcohol was given was not great. If it is not possible to produce any degenerative change by the most intensive dosage during as long a period as a month, there is little possibility that alcohol ever produces a lesion in animals that leads to cirrhosis.

Of the remaining 175 animals that received substances other than alcohol, none showed liver lesions similar to those present in human alcohol cirrhosis, except the ones that were given large doses of lead.

Lead.—The liver lesion (Fig. 2) that is produced by lethal or slightly sublethal doses of lead has been described in detail by me.[5] The hyaline net-

5. McJunkin, F. A.: The Local Action of Lead, Jour. Med. Research, 1915, 32, 271.

TABLE GIVING DATA OF AUTHOR'S ANIMAL EXPERIMENTS

No.	Animal	Number of Doses	Alcohol, per Cent.	Amount, C.c.	Period Given, Days	Liver[1]
41-45	Guinea-pig.....	32 to 78	30	5	42 to 86	Negative
46	Guinea-pig.....	12	60	4	24	Occasional necrotic cell
56	Guinea-pig.....	15	60	4	30	Negative
58	Guinea-pig.....	24	[3]	8	45	Negative
59	Guinea-pig.....	20	[3]	8	43	Negative
62	Guinea-pig.....	8	80	5	17	Negative
63	Guinea-pig.....	8	80	5	23	Negative
117	Guinea-pig.....	29	80	5	62	Negative
118	Guinea-pig.....	34	80	5	88	Negative
119	Guinea-pig.....	21	80	5	45	Negative
120	Rabbit.....	..	95[5]	0.5	..	Focal area of necrosis
124	Guinea-pig.....	23	80	5	50	Negative
125	Guinea-pig.....	23	80	5	50	Negative
126	Guinea-pig.....	23	80	5	50	Negative
127	Guinea-pig.....	88	80	5	44	Occasional necrotic cell
128-138	Guinea-pig.....	22 to 80	80	5	24 to 42	Negative
140-142	Guinea-pig.....	18 to 23	80	5	18 to 23	Negative
146	Cat.....	21	80	12	21	Negative
148	Cat.....	24	80	12	52	Negative
149	Cat.....	15	80	12	34	Few necrotic cells
150	Cat.....	11	80	12	23	Negative
152	Cat.....	6	80	12	15	Negative
153	Cat.....	7	80	12	22	Negative
154-158	Cat.....	5 to 12	95	8	10 to 62	Negative
169-175	Rabbit.....	3 to 10	80	6	6 to 11	Negative
187	Cat.....	..	80[4]	1	..	Focal necrosis
199	Guinea-pig.....	..	40[5]	5	..	Negative
200	Guinea-pig.....	..	20[6]	1	..	Negative
201	Guinea-pig.....	2	40[7]	..	2	Negative
202	Guinea-pig.....	2	40[7]	..	2	Negative
206	Guinea-pig.....	3	40	5	3	Negative
208	Guinea-pig.....	31	40	5	38	Occasional necrotic cell
210	Guinea-pig.....	1	40	5	1	Negative

1. The condition of liver is not recorded in a few cases not fixed within ten minutes after death. Immediate fixation is of the utmost importance.
2. Port wine.
3. Directly into liver. The alcohol was always given per os on a fasting stomach except when otherwise specified.
4. Injected into hepatic duct; animal killed in three days.
5. Injected into mesenteric vein; animal died immediately.
6. Injected into mesenteric vein; animal died in forty-eight hours.
7. Injected into rectum.

TABLE GIVING DATA OF AUTHOR'S ANIMAL EXPERIMENTS—(*Continued*)

No.	Animal	Number of Doses	Alcohol, per Cent.	Amount, C.c.	Period Given, Days	Liver[1]
211	Guinea-pig.....	1	40	5	2	Negative
214	Rabbit.....	10	40[8]	7	10	Negative
215	Guinea-pig.....	2	40[8]	6	3	Negative
216	Guinea-pig.....	2	40[8]	4	2	Negative
217	Rabbit.....	1	40	15	2	Negative
218	Dog.....	29	40	60	61	Negative
219	Rabbit.....	3	40	15	4	Negative
220	Guinea-pig.....	8	40	3	9	Negative
221	Rabbit.....	2	40	20	2	Surface of liver rough; microscopically marked sclerosis; negative
222	Rabbit.....	3	40	20	4	Negative
223-227	Guinea-pig.....	10 to 64	20[8]	4	23 to 72	Negative
228-231	Rat.....	3	20[8]	8	3	Negative
243	Guinea-pig[9].....	..	..	..	..	Necrotic foci involving several lobules
244	Guinea-pig[9].....	..	..	..	..	Necrotic foci involving several lobules
246	Guinea-pig[9].....	..	..	..	..	Necrotic foci involving several lobules
247	Guinea-pig[9].....	..	..	..	..	Necrotic foci involving several lobules
250	Guinea-pig[9].....	..	..	..	..	Necrotic foci involving several lobules
252-263	Guinea-pig[9].....	..	..	..	..	Necrotic foci involving several lobules
270	Rabbit.....	3	80[10]	14	14	Negative
272-278	Guinea-pig.....	8	80[10]	14	1 to 16	Negative
279	Guinea-pig.....	3	80[11]	4	6	
280	Guinea-pig.....	2	80[11]	4	6	Central necrosis
281	Guinea-pig.....	2	80[11]	4	6	
282	Guinea-pig.....	2	80[11]	4	6	Central necrosis
283	Guinea-pig.....	9	80[11]	4	30	Slight central necrosis
284	Guinea-pig.....	18	80[11]	4	54	Negative
285	Guinea-pig.....	27	80[11]	4	60	No necrosis
286	Guinea-pig.....	33	80[11]	4	60	Negative
287	Guinea-pig.....	40	80[11]	4	80	Negative
288	Guinea-pig.....	30	80[11]	4	80	Marked central necrosis
289	Guinea-pig.....	23	80[11]	4	92	Negative
290	Guinea-pig.....	23	80[11]	4	92	
291	Guinea-pig.....	44	80[11]	4	59	Negative

1. The condition of liver is not recorded in a few cases not fixed within ten minutes after death. Immediate fixation is of the utmost importance.
8. Injected subcutaneously.
9. Injected 0.25 c.c. 80 per cent. alcohol into common duct after ligation of cystic duct.
10. After chloroform anesthesia lasting two hours.
11. Alcohol containing 1 per cent. chloroform.

TABLE GIVING DATA OF AUTHOR'S ANIMAL EXPERIMENTS—(*Continued*)

No.	Animal	Number of Doses	Alcohol, per Cent.	Amount, C.c.	Period Given, Days	Liver[1]
292	Guinea-pig.....	34	80[12]	4	69	Central necrosis
293	Guinea-pig.....	34	80[12]	4	69	Central necrosis
294	Guinea-pig.....	34	80[12]	4	69	Slight central necrosis
295	Guinea-pig.....	35	80[12]	4	80	
296	Guinea-pig.....	35	80[12]	4	80	
297	Dog.....	24	80[13]	7	77	Marked central necrosis
298	Dog.....	25	80[13]	7	76	Central necrosis
299	Dog.....	14	80[13]	7	65	Central necrosis
300	Dog.....	60	80[13]	7	60	Slight central necrosis

12. With 3 per cent. chloroform.
13. With 4 per cent. chloroform.

work present in the liver cells of animals receiving lead salts blackens when treated with an alkaline sulphid. The hyalin-containing cells from cases of human cirrhosis do not give this reaction. Altogether, seventy-six animals were given lead salts and their livers examined microscopically.

Chloroform.—Fifteen animals were given chloroform in doses of sufficient size to produce slight to extensive central necrosis. These animals were used to control animals that received both alcohol and chloroform.

Pancreatin.—Twenty-nine animals received varying strengths and forms of pancreatin per os and by injection into the bile passages. The liver was negative so far as changes suggesting those present in human cirrhosis are concerned.

Bacterial Toxins.—Sixteen animals were given by the mouth the cultural products of a number of intestinal bacteria alone and in combination with alcohol. Liver negative.

Acetaldehyd.—Eight animals. Liver negative so far as changes like those present in human cirrhosis are concerned.

Formaldehyd.—Seven animals; liver negative.

Other Substances.—Pepsin, hydrochloric acid, chloral hydrate, acetone, acetic acid, sodium acetate, stannous chlorid, copper sulphate, mercuric chlorid, bismuth and Rochelle salts. Twenty-four animals; liver negative.

SUMMARY AND CONCLUSIONS

After the elimination of cases of cirrhosis of known etiology of the mechanical, infectious and syphilitic varieties, many cases fall into a class of unknown etiology. These cases appear to be of toxic origin, but differ from the central scleroses produced by known bacterial toxins and by chloroform, as well as from the cirrhosis that may follow acute yellow atrophy. Alcohol is suggested as the causative agent by the history of these cases, but there is no further evidence to indicate that it injures the liver. On the other hand, the frequently-mentioned fact that the percentage of cirrhosis among those dying

from chronic alcoholism is only slightly greater than it is among those dying from all other causes, indicates that this substance has no direct action on the liver.

A point brought out in the histologic study of a series of human cases is that there is a very active and characteristic degeneration and necrosis of liver cells present even as long as a month after the patient received his last alcohol.

A further reason for thinking that alcohol does not act directly on the liver to produce a cirrhosis is that it does not injure the liver in the lower animals. It not only does not produce a cirrhosis, but it produces no noteworthy lesion whatsoever of the liver cells.

If alcohol works no damage on the liver, or does so only indirectly, the question of the number of factors at work in the production of these cases of cirrhosis of unknown etiology arises along with the problem of the nature of the hepatic poison. In regard to the first of these questions, the uniformity of the cellular changes, especially the characteristic hyaline degeneration of the hepatic cells, and the very irregular cutting up of the lobules and islands by rather narrow sclerotic bands, point to a single causative agent or to poisons acting alike.

As to the nature of the poison, there is little evidence now at hand. Of a number of substances given to animals, lead is the only one that produces a hyaline change. The failure of the hyalin of human liver to react with an alkaline sulphid, as does that produced by lead in experimental animals, indicates that lead is not the active agent in this variety of cirrhosis. The uniformity of the lesion of these cases brought out in this study at least tends to show that there is here a variety of cirrhosis, the etiology of which is for future solution. The so-called alcoholic cirrhosis is not produced directly by ethyl alcohol, that is, the liver is not injured by the alcohol carried to it through the blood or lymph.

Fourth Street and Reservoir Avenue.

THE INFLUENCE OF THE RADIATIONS FROM KROMAYER'S MERCURY QUARTZ LAMP ON THE CEREBRAL CORTEX*

(ANIMAL EXPERIMENTS)

H. WAGO, M.D.
TOKIO, JAPAN

INTRODUCTION

Treatment by physical methods, especially by light, has been for some time a matter of common custom among clinicians; but recent progress of medical science has opened up new pathways in radiotherapy; especially have the Roentgen ray, radium ray, and ultraviolet ray been put on a more scientific foundation.

In general, they all have a destructive action on living cells, but each has its special characteristics; in therapy it is desirable to make the best use of these special characteristics.

I believe that up to the present there has not been an efficient study of the characteristics, actions and influences of the ultraviolet radiations. I determined to study their action on the cerebral cortex of rabbits. I employed to produce them, Kromayer's mercury quartz lamp, as the radiations from it consist of a very high percentage of ultraviolet rays and a low percentage of violet and blue rays.

1. *Kromayer's Mercury Quartz Lamp.*—The mercury quartz lamp is an outgrowth of the mercury vapor light, investigated by Arons in 1892, and found to give a light very rich in chemical rays, especially the ultraviolet; but these rays are absorbed by the glass, so that the light which passes through the glass tube has no pathologic influence on tissues.

Küch, therefore, made the apparatus with quartz instead of glass; for, not only can all the ultraviolet rays radiating from the mercury quartz lamp pass through, but there is a strong resistance for the high heat; but more or less heated light still passed through the apparatus, so Kromayer modified it in 1904, ridding it of the heated light by adding a cooling apparatus. So this apparatus is called Kromayer's mercury quartz lamp (*Kromayer'sche Quecksilberquartzlampe*).

2. *Actions of the Radiations from the Mercury Quartz Lamp.*—Because the radiations from the mercury quartz lamp have irritative and disinfecting actions, Kromayer reported in 1906 the experimental results of his study of the radiations. He noted (1) that the

* Submitted for publication Nov. 7, 1916.

radiations caused inflammatory and disinfective action of the skin; (2) that they could be made to invade the deeper tissues; (3) that the strength of these actions was in direct proportion to the quantity of the electric current used to produce the radiations.

A. *Irritative Action of the Radiations.*—The irritative action of the radiations is inversely proportional to the distance; that is, when at a distance, only slight inflammation of the skin is produced; but when the apparatus is in pressure contact with the skin the result is disturbance of the deeper tissues (much of the radiation is absorbed by the blood, consequently when the apparatus is in pressure contact with the skin a local anemia is produced by the pressure, and the rays are not absorbed), and the degree of disturbance is in direct proportion also to the radiating time.

Thus the disturbances produced are in direct proportion to both time of radiation and quantity of current lost, and inversely proportional to the distance.

B. *Disinfective Action of the Radiations.*—Downes and Blunt, in 1877, were the first to investigate the disinfective action of the ultraviolet rays, and afterward Courmont and Nogier, in 1909, studied the action in detail.

In general, the sensitiveness of bacteria to the ultraviolet rays differs with the variety; according to the studies of Cernovodeau and Herni, the disinfective action of the radiations from the mercury quartz lamp on many bacteria are as follows:

(*a*) The water examined had 10,000 to 100,000 bacteria per 1 c.c. before it was radiated.

(*b*) The electric current used to produce the radiations was of 110 volts and the lost quantity was 3 amperes.

(*c*) The distance to the surface of the water from the apparatus was 20 cm.

(*d*) Time in seconds required to sterilize the water completely:

	Seconds		Seconds
Staphylococcus	5 to 10	Vibrio cholerae	10 to 15
B. typhosus	10 to 20	B. dysenteriae	10 to 20
B. coli-communis	15 to 20	Diplococcus pneumoniae	20 to 30
B. anthracis	20 to 30	B. tetani	20 to 60
B. subtilis	30 to 60		

C. *Chemical Action of the Radiations.*—The chemical action of the radiations is very strong, and according to von Behring's studies, 10 per cent. chinone-alcohol solution may be turned black in four minutes, and 20 per cent. vanilin-alcohol solution brown in six minutes; besides these, it has many other reactions.

D. *Sensitiveness of the Human Body to the Radiations.*—It is said that the sensitiveness of the human body to the radiations is indefinite, and it is impossible to determine just the fit quantity for use, as in the case of the Roentgen ray.

EXPERIMENTAL RESEARCHES

My own experimental researches on the influence of the radiations, especially the ultraviolet from the mercury quartz lamp, on the cerebral cortex of rabbits, are as follows:

A. *The Methods.*—Rabbits only were used in these experiments. A selected part of the head was prepared, the hair cut, the skin sterilized with alcohol, and then incised aseptically, the periosteum stripped from the cranium, the bone trephined and a piece of bone removed. Sutures were taken first in the stripped-up periosteum and then in the skin. The wound was covered with collodion and left to heal for about two days before radiating. Care was taken not to wound the brain substance during the operation.

The trephine which I used was 0.8 cm. in diameter; the part trephined was one side of the occiput; the other side was preserved for the control; the radiation was that from the mercury quartz lamp, produced with 3 amperes of direct current; the radiating method was the direct, and the radiated time was 10, 20, 30 and 60 minutes, respectively.

B. *Macroscopic Changes Caused by the Radiations.*—The macroscopic changes caused by the radiations, using the foregoing methods, are as shown in the accompanying tables:

TABLE 1.—DATA OF EXPERIMENTS WITH THE RADIATIONS

No. of Experiment	Sex	Weight of Body, Gm.	Trephined Part	Radiating Method	Time of Each Radiation, Minutes	The Strength of Radiations
1	Female (pregnant)	2,585	Right occiput.	Direct....	10	The radiations caused by 3 amperes of the direct current with resistance No. 1 attached to Kromayer's mercury quartz lamp. The resistance was made in Japan.
2	Male.....	1,955	Left occiput...	Direct....	20	
3	Male.....	2,060	Right occiput.	Direct....	30	
4	Female.....	2,455	Right occiput.	Direct....	60	
5	Female (23 days old)	345	Right occiput.	Direct....	10	
6	Male (23 days old)	350	Not trephined.	Radiated on the right	30	
7*	Male.....	900	Right occiput.	Not radiated	..	
8*	Male.....	2,165	Not trephined.	Not radiated	..	

* Control.

C. *Control Examinations.*—(Experiments 7 and 8.) As controls I used two rabbits in good health which were not radiated.

EXPERIMENT 7.—In this case I trephined the right occipital region, but did not radiate; the rabbit was killed with chloroform on the seventeenth day after the trephining, and examined for histologic changes in the part of the brain trephined; there were no changes.

EXPERIMENT 8.—In this case I did not trephine or radiate; the rabbit was killed with chloroform, and a histologic examination made of the occipital portion of the brain.

D. *The Macroscopic Appearances of the Trephined Part.*—At the trephined opening new bone developed from the periosteum, and the skin radiated was thickened more or less.

E. *The Histologic Study of the Tissues Radiated.*—Histologic study was made by the following methods: 1. Fixing Fluids: (a) 10 per cent. formaldehyd solution; (b) Müller's fluid. 2. Mounting Methods: (a) celloidin mounting;

TABLE 2.—Data of Experiment on Radiations

No. of Experiment	No. of Treatment	Time of of Radiating, Minutes	Weight of Body Gm.	Remarks
	1	10	2,575	No changes.
	5	10	2,455	Miscarried, five rabbits with four treatments (on the fifth day after the first treatment)
	6	10	2,380	At the radiated part, baldness began to appear; its area was as large as a nickel (after six treatments
1	7	10	2,550	Baldness was noted
	12	10	2,305	Regeneration of hair on the bald part began on the eighth day after the loss of hair had begun. Paralysis was noticed in the left forefoot after sixteen treatments (on the twenty-eighth day)
	17	10	2,440	Paralytic condition was noted
	18	10	2,475	Paralytic condition was noted
	24	10	2,550	Paralytic condition was noted
		0	2,370	Killed with chloroform on the thirty-seventh day after the first treatment
	24	4 hrs.		
	1	20	1,920	No changes
	3	20	2,025	Paralysis was noticed in the right forefoot after two treatments (on the third day)
	4	20	2,075	Paralytic condition noted
	7	20	2,085	The paralytic condition was the same; and at the radiated part, baldness began to appear and its area was as large as a nickel (after seven treatments)
2	8	20	2,050	Baldness was noted
		0	2,045	Regeneration of hair on the bald part began on the ninth day after the loss of hair had begun; the paralytic condition was the same
		0	2,065	The paralytic condition was the same; animal killed with chloroform on the 32d day after first treatment
	8	2 hrs. 40 min.		
	1	30	2,080	No changes
	2	30	2,240	Paralysis was noticed in the left forefoot the twenty-second hour after the first treatment
	3	30	2,185	Paralytic condition was noted
3	6	30	2,125	The paralytic condition was the same; and at the radiated part baldness began to appear and its area was as large as a nickel; the skin of this part was thickened notably (after six treatments)
		0	2,115	The paralytic condition was the same, and regeneration of hair on the bald part began on the seventh day
		0	2,115	The paralytic condition was the same; animal killed with chloroform on the thirty-first day after the first treatment
	6	3 hrs.		
	1	60	2,300	No changes
	2	60	2,470	Paralysis was noticed in the left forefoot the twentieth hour after the first treatment
4		0	2,510	Paralytic condition noted; at the radiated part baldness began to appear on the sixth day after the first treatment; its size was the same as in No. 1
		0	2,515	The paralytic condition was the same; regeneration of hair on the bald part began on the seventh day
		0	2,530	The paralytic condition was the same; animal killed with chloroform on the twenty-first day after the first treatment
	2	2 hrs.		

TABLE 2—*Continued*

No. of Experiment	No. of Treatment	Time of of Radiating, Minutes	Weight of Body Gm.	Remarks
	1	10	340	No changes
	2	10	350	Paralysis was noticed in the left forefoot the twenty-fourth hour after the first treatment
	3	10	370	Paralytic condition noted
5	7	10	480	The paralytic condition was the same; at the radiated part baldness began to appear after six treatments (on the seventh day); its size was the same as in No. 1
	8	10	450	The paralytic condition was the same; at the radiated part baldness began to appear after six treatments (on the seventh day); its size was the same as in No. 1
		0	467	The paralytic condition was the same; regeneration of hair on the bald part began on the sixth day
		0	498	The paralytic condition was the same; animal killed with chloroform on the thirty-first day after the first treatment
	8	1 hr. 20 min.		
	1	30	350	No changes
6	7	30	500	No changes
		0	550	No changes; animal killed with chloroform on the thirty-first day after the first treatment
	7	3 hrs. 30 min.		

(b) paraffin mounting; (c) Fukushi's (Japanese) gelatin mounting; (d) freezing method. 3. Thickness of the sections, 5 or 6 microns.

4. Staining Methods: (a) hematoxylin-eosin double staining; (b) Lenhossek's staining for ganglion cells; (c) Nissl's staining for ganglion cells; (d) Bielschowsky's staining; (e) Marchi's staining; (f) Taumura's (Japanese) staining for the neurilemma and axis-cylinder; (g) fat staining with sudan III.

MICROSCOPICAL EXAMINATIONS

A. Histologic examination of the radiated part of the cerebral cortex (Experiments 1 to 6).

EXPERIMENT 1:

1. The molecular layer.

There were seen no pathologic changes.

2. The layer of small pyramidal cells.

In general, the nerve cells of the superficial part of this layer were atrophied, and the cells of the deeper part close to the layer of the large pyramidal cells were swollen. Most of the swollen cells showed a perinuclear chromatolysis and vacuolation of the cytoplasm at their periphery; some cells burst because of the great swelling; some showed a displacement of the nucleus; some showed the phenomena of karyolysis, karyorhexis and pyknosis of the nuclei. In general, those cells which showed karyolysis and those which were destroyed, reacted very weakly to the staining solutions. Such phenomena as chromatolysis, karyolysis, karyorhexis, displacement of the nucleus, vacuolation and swelling of nerve cells were very marked in the deeper parts; in the superficial parts there was seen only contraction.

3. { The layer of large pyramidal cells.
   { The layer of polymorphous nerve cells.

The pathologic changes in both of these layers generally resembled the

changes in the layer of small pyramidal cells, but their degree was much greater than in the second layer. In these four layers there was seen no fatty degeneration of the nerve cells or any degeneration of the neurofibrils, but a slight infiltration of small round cells.

EXPERIMENT 2:

1. The molecular layer.

There were seen no pathologic changes.

2. The layer of small pyramidal cells.

The pathologic changes in the nerve cells of this layer generally resembled those of the second layer of Experiment 1, but in lesser degree. The nerve cells of the superficial part were atrophied less than those of Experiment 1; those of the deeper part were in general swollen and the nuclei were degenerated, but the vacuolation was slight.

3. The layer of large pyramidal cells.
   The layer of polymorphous nerve cells.

The changes in both layers resembled the changes in the deeper part of the layer of small pyramidal cells of Experiment 1; but in this case (1) there were seen many nerve cells with less protoplasm, because the nucleus was notably swollen; and (2) in other cells the nuclei were destroyed and the bodies of the cells vacuolated; in this case, also, the pathologic changes in the nerve cells were greater in the deeper part than in the superficial part. In all layers there were seen no fatty degeneration of the nerve cells or any degeneration of the neurofibrils, but a slight infiltration of small round cells.

EXPERIMENT 3:

1. The molecular layer.

There were seen no pathologic changes.

2. The layer of small pyramidal cells.
3. The layer of large pyramidal cells.
4. The layer of polymorphous nerve cells.

In general, the pathologic changes of these three layers resembled the changes of those of Experiment 1, but much greater in degree; for example, many nerve cells were atrophied, especially in the layer of small pyramidal cells; the number of swollen cells was increased in the deeper part and the cell bodies were notably vacuolated. The nuclei of some of the vacuolated cells was already destroyed. In some of the swollen cells at the deeper part the volume of protoplasm, because of the swollen nuclei, was greatly diminished. In general, the superficial cells were atrophied, while the deep cells were swollen and vacuolated. In none of the layers was there seen any fatty degeneration of the nerve cells or any degeneration of the neurofibrils, but a slight infiltration of small round cells.

EXPERIMENT 4:

1. The molecular layer.

There were seen no pathologic changes.

2. The layer of small pyramidal cells.
3. The layer of large pyramidal cells.
4. The layer of polymorphous nerve cells.

In general, the pathologic changes in the nerve cells in these three layers resembled, but were less than, the changes of those of Experiment 3. The nerve cells of these three layers were generally swollen and some of them vacuolated, and also some of the cells of the first layer were atrophied. The changes of the cytoplasm and nucleus were the same as those of Experiment 3.

In this case, also, in none of the layers was there seen any fatty degeneration of the nerve cells or any degeneration of the neurofibrils, but a slight infiltration of small round cells.

EXPERIMENT 5:

1. The molecular layer.

There were seen no pathologic changes.

2. The layer of small pyramidal cells.
3. The layer of large pyramidal cells.
4. The layer of polymorphous nerve cells.

The pathologic changes of the nerve cells in these three layers were about the same as those of Experiment 4, but in this case the nerve cells were swollen only in the layer of polymorphous nerve cells; in the layer of small pyramidal nerve cells there was more or less atrophy. The vacuolation of the cytoplasm was seen in the third and fourth layers, and in a very few instances in the second layer; also there were seen a few cells which were already destroyed and which showed a diffuse, homogeneous staining of their bodies.

In none of the layers was there seen any fatty degeneration of the nerve cells or any degeneration of the neurofibrils, but a slight infiltration of small round cells. In short, in this case, the degree of the pathologic changes is moderate.

EXPERIMENT 6:

1. The molecular layer.

There were seen no pathologic changes.

2. The layer of small pyramidal cells.
3. The layer of large pyramidal cells.
4. The layer of polymorphous nerve cells.

Some of the nerve cells in these three layers were swollen and chromatolyzed more or less, but the degree of the changes was much less than in those noted previously; and none of the other changes was recognized.

B. Histologic examination of the control part (Experiments 1 to 6).

In none of these layers were there found any pathologic changes.

EXPERIMENT 7: (Control examination.)

In the histologic examination of the trephined and control parts there were found no pathologic changes in either.

EXPERIMENT 8: (Control examination.)

In this case there was no change, because the animal was in good health and used only for the control examination.

SUMMARY

Following is a summary of facts found in the foregoing experiments.

1. The radiations used for the experiment were produced from Kromayer's mercury quartz lamp, 3 amperes of the direct current being used, with resistance No. 1 attached to the apparatus.

2. The strength of the radiations was the same in all cases.

3. The radiating method was "the direct" in each case.

4. The results of Experiment 1 were: miscarriage after four treatments (forty minutes) on the fifth day; paralysis of the left fore foot after sixteen treatments (two hours and forty minutes) on the twenty-eighth day; the degree of the paralysis became greater with each treatment. As to the microscopic pictures of the cerebral cortex, in general, the nerve cells in the superficial part were atrophied, but the cells in the deeper part were swollen and presented the phenomena of chromat-

olysis, displacement of the nucleus, karyolysis, karyorhexis and vacuolation.

5. In Experiment 2 the results were: paralysis of the right fore foot after two treatments (forty minutes) on the third day. The degree of paralysis became greater with each treatment. As to the microscopic pictures of the radiated part of the cerebral cortex, they resembled those of Experiment 1, but were less in degree.

6. In Experiment 3 the results were: paralysis of the left fore foot after two treatments (one hour); this condition was noticed the twenty-second hour after the first radiation, and the degree of the condition became greater with each treatment. As to the microscopic pictures of the radiated part of the cerebral cortex, they resembled those of Experiment 1, but the changes were more marked.

7. In Experiment 4 the results were: paralysis of the left fore foot after two treatments (two hours); this condition was noticed the twentieth hour after the first radiation. The microscopic pictures of the radiated part of the cerebral cortex resembled those of Experiment 3, but were less in degree.

8. In Experiment 5 the results were: paralysis of the left fore foot with two treatments (twenty minutes), and this condition was noticed the twenty-fourth hour after the first radiation; the degree of the paralysis became greater with each treatment. The microscopic pictures of the radiated part of the cerebral cortex resembled those in Experiment 4, but the changes were more marked.

9. In Experiment 6 the rabbit was only 23 days old and was radiated without trephining for purposes of control. Macroscopically, there were no changes; as to the microscopic pictures of the radiated part of the cerebral cortex, in general, the nerve cells throughout the second to the fourth layers were swollen more or less, and a few of them presented the phenomena of chromatolysis.

10. Experiment 7 was performed to determine whether or not paralysis of the foot would result from trephining without radiating, as a control examination; there were recognized no macroscopic or microscopic changes.

11. In Experiment 8 a rabbit in good health, without trephining or radiation, was used for the microscopic examination of the occipital cortex as a control.

12. In the tissues of the control parts in Experiments 1 to 6 there were no changes.

13. Surface effect at the radiated part: Baldness was noticed about seven days from the first radiation, but there was a regeneration of

hair about seven days later (in Experiments 1 to 5); in Experiments 6 and 7 there was not such a process.

14. In the trephined part new bone developed from the periosteum; the radiated skin was thickened more or less.

15. The weight of the body during the experiment in each instance was almost without change.

CONCLUSIONS

While it is generally believed that the action of the Roentgen ray on the central nervous system is very weak, the action of the radiations from Kromayer's mercury quartz lamp is remarkably strong, and the effects are due to the ultraviolet rays, which are the chief constituents of the radiations. The effect of the radiations on the cerebral cortex of the rabbits experimented on was as follows:

1. The strength of the action of the radiations is in proportion to the time of radiation.

2. The effect of the radiations on the cerebral cortex is the disturbance of the nerve cells as heretofore mentioned; that is, the production of swelling, atrophy, chromatolysis, karyolysis, karyorhexis, displacement of nucleus, vacuolation and cell death.

3. As shown by Experiments 1 to 5, the retrogressive processes in the nerve cells begin, at first, with the superficial part of the cerebral cortex, and gradually progress into the deeper part.

4. The resistance of the cerebral cortex of the young rabbit against the radiations is very much weaker than in case of old rabbits, as shown in Experiments 5 and 6.

5. The paralytic condition of the fore foot of the experimented animals is due to the results of the retrogressive processes in the nerve cells.

6. No pathologic changes in the neurofibrils could be recognized, even after the nerve cells had notably degenerated, but it is believed that the neurofibrils suffer some degenerations on account of the retrogressive processes in the nerve cells.

7. The radiations may more or less pass through the cranium of the very young rabbit, as indicated by Experiment 7.

8. It is impossible to determine just what quantity of radiations is needed for proper use, as in the case of Roentgen rays.

9. In Experiments 1 to 5 the baldness produced at the radiated part of the experimented animals was due, it is believed, to the temporary disturbances of nutrition of the skin, because of the failure of the skin to unite with the surrounding tissues over the trephine wound, and also because of the pressure on the blood vessels at that part by

the Kromayer apparatus. The process of regeneration of hair which followed on the bald spot was due to the irritative action of the radiations.

10. The thickening of the skin at the radiated part is due to the chronic irritative action of the radiations.

This work was carried out at the laboratory of St. Luke's Hospital, Tokio, Japan, in September, 1915, and it is a great pleasure to express to Dr. Y. Kon, professor of pathology at the Tokio Charity Hospital Medical College, my sincerest thanks for his many helpful suggestions and aid given to me in carrying out the details of this study; and also to express my gratitude to Dr. E. Iida, head of the department of dermatology at St. Luke's Hospital, for permission to use the Kromayer mercury quartz lamp.

BIBLIOGRAPHY

1. Kromayer: Deutsch. med. Wchnschr., 1906, Nos. 10 and 22.
2. Axmann: Deutsch. med. Wchnschr., 1906, No. 15.
3. Schüler: Deutsch. med. Wchnschr., 1906, No. 17.
4. Wangemann: Elektrotechnischer Anzieger, 1904, Nos. 78, 79 and 80.
5. Japanese medical books and journals:
   A). Dohi, K.: Physical Therapy; General Dermatology.
   B). Dohi, Shoji: Jour. Skin and Venereal Dis., **13,** Nos. 6 and 9.
   C). Dohi; Mine: Jour. Skin and Venereal Dis., **12,** No. 3.
   D). Honda: Jour. Army Med. Soc., No. 170.
   E). Nishizawa: Jour. Army Surg. Soc., No. 35.

THE REFLEX ACTION OF VOLATILE IRRITANTS ON THE CIRCULATION *

C. C. LIEB, M.D., AND W. W. HERRICK, M.D.
NEW YORK

Among the measures in common use in combating conditions of threatened or actual circulatory failure, is the subcutaneous or intramuscular injection of volatile substances of a highly irritant nature. Among these so-called circulatory stimulants are ether, alcohol in the form of whisky or brandy, and camphor dissolved in ether, alcohol, or oil. The clinical use of these substances in shock and allied conditions is based, not on exact experimental observation, but on casual bedside impression and tradition.

OBJECT OF THE EXPERIMENTS

As a result both of laboratory observation and clinical experience, we have for some time held the opinion that the effects of the injection of volatile irritants were due, not to a direct stimulation of the circulation, but to a reflex action arising from intense irritation of sensory nerve endings. That intense irritation or stimulation of a sensory nerve may lead to a reflex rise in blood pressure has been known for a long time, but as far as we have been able to ascertain from the literature, this explanation of the action of volatile irritants is not the one ordinarily offered. If this group of substances acts in the manner suggested, the importance of a critical study of measures so universally used by clinicians becomes at once apparent. Any change in the circulation following the employment of these drugs is brought about by excitation of the medullary centers by afferent impulses, initiated at the site of injection. A rise in blood pressure presupposes a vasomotor center which is capable of excitation. These drugs are used almost exclusively in the treatment of shock and collapse — conditions in which the center is believed either to be paralyzed, and therefore incapable of excitation, or to be so active that further stimulation of the center does not bring about any large increase of blood pressure. In either case bombardment of the vasomotor center by afferent stimuli will result in no material increase in blood pressure. Furthermore, the pain at the site of injection may lead to a deepening of the shock or collapse already present.

* Submitted for publication Nov. 14, 1916.

* From the Department of Pharmacology, College of Physicians and Surgeons, Medical Department of Columbia University.

EXPERIMENTAL STUDY OF ACTION OF VOLATILE IRRITANTS

Technic.—All the experiments were performed on cats, decerebrated under ether, the temperature of the animal being maintaind by an electric pad. An interval of at least twenty minutes was allowed to elapse between decerebration and the beginning of the experimental record, so that the ether was completely eliminated and reflex irritability restored. Such an animal is incapable of feeling pain. It breathes spontaneously, but in effect is nothing but a reflex machine.

It is worthy of note that the reflex irritability of an animal is greatly increased by destruction of the cerebral hemispheres. Hence the response to a given stimulus is much more pronounced in decerebrate animals than in normal individuals.

TABLE 1.—DATA OF—

Substance	Abdomen	Chest Wall	Leg (Thigh)	Hand
Ringer's solution	I* 2	I 0	.....	II 0
Water	I 1	I 0	II 3.5	II 10
Alcohol	I 0	I 0	I 0	VII 17.3
Ether	I 0	.....	I 0	VIII 17.6
Camphor and ether	I 0	II 4	II 4	XI 9.5
Turpentine	III 0	II 5	II 0.5	XL 8.1
Camphor and oil	.....	II 0	II 0	III 13.7
Total injections	VIII	IX	X	LXXIII
Average rise in blood pressure	0.4	2	1.6	10.3

* Roman numerals indicate the number of injections. Arabic numerals indicate the

For the injections, a glass syringe equipped with a 28-gage needle was used. A needle of such small caliber causes a minimum of local trauma—a factor of importance in estimating the reflex irritant effect of the substance introduced into the tissues through the needle. As a further precaution, the effect on blood pressure of the introduction of the needle alone was observed and an interval of several seconds allowed to elapse between the penetration of the tissues by the needle and the injection of the irritant. In many instances in which the animal was more than ordinarily irritable, the puncture of the skin by the small needle was followed by a rise in blood pressure, or by convulsive movements. These effects were similar to, though less than, those brought about by the irritant injections themselves.

Substances Used.—These were the usual volatile irritants employed in clinical work; ether; camphor, 10 per cent. in ether; camphor, 20 per cent. in oil; "spirits of camphor," (camphor, 10 per cent. in alcohol); whisky; and in addition, oil of turpentine. The latter was chosen because it is an intense irritant without immediate grave toxic effects. Ringer's solution, distilled water and tincture of digitalis also were used.

TABULATED RESULTS

The results are presented in tabular form in order to avoid detailed report of protocols. These tables are arranged to show the effect on blood pressure of: (1) the substance injected; (2) the site of injection (3) the comparative effects of the different volatile irritants.

In compiling these tables from the protocols, it is realized that comparison of quantitative results is not strictly allowable, since the experimental conditions were so variable. However, only those experiments are used in which conditions were usual — the animal having intact reflexes, not having suffered impairment of the central nervous system through asphyxia, faulty technic in decerebration, etc. As the total number of injections was large, the average figures have some value, however inexact.

—Author's Experiments

Foot	Nose	Dorsum of Foot	Muscle	Arm	Total Injections and Average Rise in Blood Pressure
I 0	.....	.....	.....	I 0	VI 0.3
.....	.....	.....	.....	.....	VI 3.6
II 1	.....	.....	.....	.....	XII 2.6
IX 5	I 28	.....	.....	.....	XX 10.1
XIX 18.5	I 21	I 34	.....	.....	XXXVII 13.0
XXXI 9.9	II 12.5	I 18	I 7	.....	LXXXII 7.6
I 8	.....	.....	.....	.....	VIII 5.3
LXIII	IV	II	I	I	
11.3	18.5	26	7	0	

average rise in blood pressure.

SITES OF INJECTION

Reference to Table 1 shows that irritants were injected under the skin of the following regions: pads of the hands and of the feet, thighs, forearm, abdomen and chest wall. A number of injections were also made into the submucous tissue of the nasal septum. Of these regions the submucosa of the nose seemed to be the most irritable, since the reflex rise in blood pressure was the greatest. That this rise in blood pressure was not due to partial asphyxia as a result of the manipulation, is proved by the fact that after tracheotomy similar increase in blood pressure occurred on injection into the nasal submucosa.

Next in degree of sensibility are the pads of the hands and feet. When injections are made under or into the pads, a prompt and considerable rise in pressure usually occurs. It is interesting to note that the rise in blood pressure following injection into the pads of the feet, is somewhat greater than that following injections of similar doses into the pads of the hands.

The least sensitive areas seem to be the subcutaneous tissue of the

general body surface, for injection into these tissues results in practically no change in blood pressure. In this connection it may be pointed out that decerebrated animals are incapable of appreciating pain, hence changes in blood pressure following the injection of irritant substances are due solely to the reflex action on the vasomotor centers. On the other hand, in intact, unanesthetized animals, such injections are extremely painful and rise in pressure may occur as a result of this disturbance of consciousness.

It may be permissible to conclude from these experiments that the order of sensibility of the various regions injected is as follows: (1) nasal septum; (2) pads of feet; (3) pads of hands; (4) the general body surface. These results are in accord with the observations of von Frey[1] and of Crile[2] on the comparative sensibility of various parts of the body surface.

RELATIVE IRRITABILITY OF THE VARIOUS SUBSTANCES USED

The irritating character of a substance depends partly on its volatility, partly on osmotic tension, its ability to coagulate protein, and on other inherent and less well defined qualities. Ether, alcohol, and turpentine are volatile substances and seem irritant in proportion to their volatility. The irritant character of ether may be enhanced by having camphor in solution. Oil is by no means a bland substance when brought into direct contact with the sensory nerve-endings in the skin. Camphor in solution doubtless increases the irritant effects of the oil. Water is irritant largely through its alteration of the osmotic relations of the parts injected. Aside from other physical factors, all subcutaneous injections are painful by reason of the local tension brought about. In an injection of a fluid like Ringer's solution, only the last named factor comes into play. Judging from the degree of response, in the way of rise in blood pressure, from subcutaneous injection of the substances used, the order of irritability is as follows: Ringer's solution, practically non-irritant; distilled water, alcohol, equally irritant; camphor in oil, turpentine, ether, camphor in ether. (See Table 1.)

DURATION OF EFFECT

The total duration of the response to the injection was usually less than fifteen minutes. A typical reaction is shown in Figure 1. At the first signal the needle of the hypodermic was plunged through the skin

1. Von Frey: Starling, "Human Physiology," 1915, p. 490.
2. Crile, G. W.: "Surgical Shock," Philadelphia, 1899, p. 122, et seq.

covering the center pad of the right foot. Three seconds later, at the second signal, 1 c.c. of oil of turpentine was injected. A few seconds after the injection was begun blood pressure began to rise. The maximum rise, which was about 16 mm. of mercury, was reached in three seconds and was followed by a *quick* fall of about 10 mm. At this point blood pressure was still 6 or 8 mm. above normal. The pressure now fell more gradually, so that the normal pressure was regained twelve minutes after injection. In a small percentage of the experiments the rise in blood pressure was followed by an abrupt fall to normal, so that the entire reaction lasted less than two minutes. (See Figure 3, A, experiment of Dec. 3, 1915.) The extreme transientness of the complete cycle suggests that the therapeutic use of these substances is very limited.

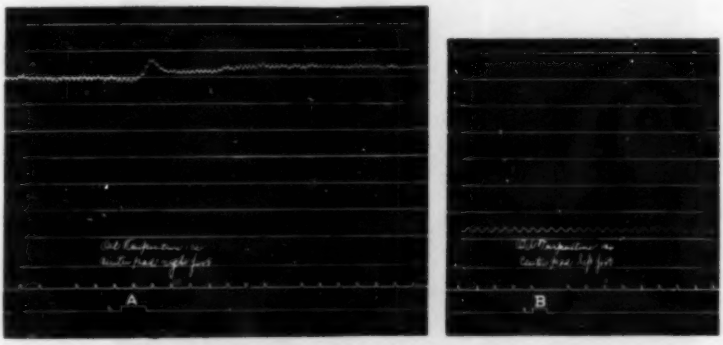


Fig. 1.—Cat decerebrated under ether. At A, 1 c.c. of oil of turpentine was injected into the center pad of the right foot; nerve supply intact. At B, 1 c.c. of oil of turpentine was injected into the center pad of the left foot; entire central nervous system had been destroyed. In this and the subsequent tracings the lowest line serves as a signal; the next above gives time in five-second intervals, the third line from the bottom corresponds to the zero of blood pressure.

RATE OF INJECTION

The effect on blood pressure seems to be directly proportional to the intensity of the irritation. Figure 2, experiment of Dec. 29, 1915, shows at B the effect of the injection of 1 c.c. of oil of turpentine into the center pad of the right hand. The time occupied by the injection was approximately three seconds. The first part of the tracing at A shows the effect on blood pressure when the same amount of oil was injected into the corresponding pad of the other hand. The only difference in technic is the time required to complete the injection. Injection B occupied approximately three seconds, whereas Injection A required 110 seconds. In one case, irritation is sudden and sharp and is followed by a profound change in blood pressure; in the other, irritation is mild and prolonged and causes no rise in blood pressure.

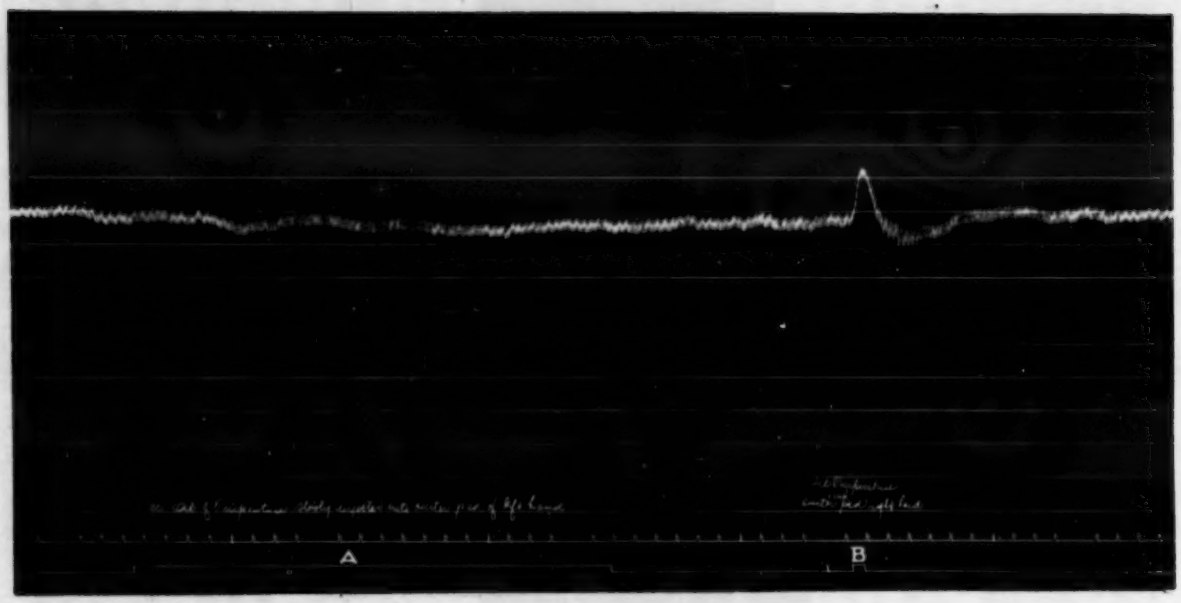


Fig. 2.—Cat decerebrated under ether. At A, 1 c.c. of oil of turpentine was injected into the center pad of the left hand; time required to complete injection, 110 seconds. At B, 1 c.c. of oil of turpentine was injected into the center pad of the right hand. Injection time, three seconds.

REPEATED INJECTIONS

In some of the earlier experiments, in which camphor and ether were injected at short intervals, it was found that there was throughout the experiment a gradual and progressive fall of the average blood pressure. At the same time, successive doses of camphor and ether produced relatively smaller and smaller increases in blood pressure. To account for this a number of explanations suggested themselves. In the first place, the effects might be due to the gradual paralysis of the vasomotor center by the progressive accumulation of ether; or they might be the result of exhaustion of the vasomotor center from repeated afferent stimulation; in other words, we might be dealing with a form of traumatic shock; or, finally, the repeated excitation of the same nerve paths might result in their exhaustion. The direct paralytic action of the irritants on nerve-endings was excluded, since no two injections were made into exactly the same site. That the gradual depression of blood pressure was the result of the accumulation of ether was shown by the experiment of Dec. 14, 1915.

Successive doses of 1 c.c. of camphor and ether were injected into different pads of the feet and hands. The first injection was followed by a rise in blood pressure of 12 mm.; the second, five minutes later, resulted in a rise of 10 mm.; the third, five minutes later, gave a rise of 20 mm.; the fourth, after a five-minute interval, gave a rise of 8 mm.; the fifth injection, six minutes later, gave no rise; neither did the sixth, seven minutes later; nor the seventh, five minutes later. In two experiments of Dec. 17, 1915, in which ether 1 c.c. was injected at intervals of ten minutes, thus allowing time for the elimination of ether, the blood-pressure response to the later injections was not lessened.

In other words, if ten minutes be allowed to elapse between injections of 1 to 2 c.c. of ether, no progressive fall in blood pressure occurs. If injections are repeated at two minute intervals, ether accumulates in the organism and prevents reflex blood pressure response.

Because of the danger of ether's depression of the central nervous system and the consequent masking or abolition of reflex effects, recourse was had to oil of turpentine. This volatile oil is highly irritant and causes stimulation of the medulla and spinal cord. Hence, one might expect not a progressive loss, but a progressive increase of irritability, resulting eventually in convulsions. With this substance, repeated injections led to no marked permanent fall in blood pressure, and no marked change in the degree of the vasomotor response to repeated injections until convulsions developed.

SHOCK FROM REPEATED INJECTIONS

The possibility of inducing shock by the repeated traumatism of irritant injections was studied in a few instances. Oil of turpentine was chosen because its toxic effects are comparatively slow in appearing, while the irritant effects are marked and immediate. Collapse could

not be induced before the convulsions of the toxic stage of turpentine action appeared.

In the experiment of Feb. 1, 1916, 23 injections of oil of turpentine, 1 c.c. each, were given in the course of the experiment. Injections 1 to 9, inclusive, were followed by rise in blood pressure varying from 20 to 2 mm. Injections 20 to 23, inclusive, were not followed by any rise in blood pressure. A terminal asphyxial rise of blood pressure showed that the vasomotor center was not paralyzed. Beginning with Injection 15, there were signs of turpentine poisoning, namely, vomiting and convulsive movements. No signs of collapse appeared in this animal.

THE EFFECT OF SUCCESSIVE INJECTIONS INTO THE SAME REGIONS

This phase of the study involves the question of the effect on the nerve-endings of the site of injection, and the reflex arc. A short though variable time, usually not less than two minutes, is required for the recovery of a degree of irritability of the nerve-endings at the site of injection.

TABLE 2.—EXPERIMENT OF DECEMBER 17: INJECTION OF 1 C.C. CAMPHOR 10 PER CENT. IN ETHER

Number of Injection	Time of Injection	Site	Change in Blood Pressure, Mm.
I	2:35	Second pad of right foot	+ 20
III	2:15	Second pad of right foot	+ 20
II	2:55	Third pad of right foot	+ 18
IV	2:30	Third pad of right foot	+ 10
V	2:38	Center pad of right foot	+ 11
VI	2:25	Center pad of right foot	+ 10

It will be noted that in the experiment of December 17 there was exhaustion neither of the nerve endings nor of the reflex arc from successive injections into the same site or sites involving approximately the same reflex arc. The recovery of irritability of nerve endings is shown to be prompt and to take place in less than two minutes (see Injections V and VI).

In several similar experiments with different irritants, corresponding results were obtained.

THE NATURE OF THE RESPONSE

Our original hypothesis was that the reaction to the subcutaneous injection of an irritant is reflex in origin. The impulses arise at the point of injection, pass along the afferent nerves to the central nervous system and excite the vasomotor center. If this assumption is correct, any procedure which interrupts this arc will prevent the development of the reflex rise in blood pressure.

1. Cutting of the Afferent Nerves.—Section of sensory nerves prevents the usual rise in blood pressure when an irritant is injected into the denervated area.

In the experiment recorded in Figure 3, at A, 1 c.c. oil of turpentine was injected into a pad of the left foot. There was an immediate rise of blood pressure of 38 mm. A similar injection into the central pad of the right foot also caused a rise of 38 mm. The left sciatic and crural nerves were then cut. Five minutes later at B, Figure 3, 1 c.c. of oil of turpentine was injected into a foot pad of the denervated left leg. Blood pressure remained constant at the previous level.

This experiment shows that when afferent impulses are prevented from reaching the vasomotor center the injection of volatile irritants fails to cause a rise in blood pressure. The fact that the injection into the left leg caused the usual response, indicated that the vasomotor center was active and capable of stimulation. Like results were obtained in a number of experiments.

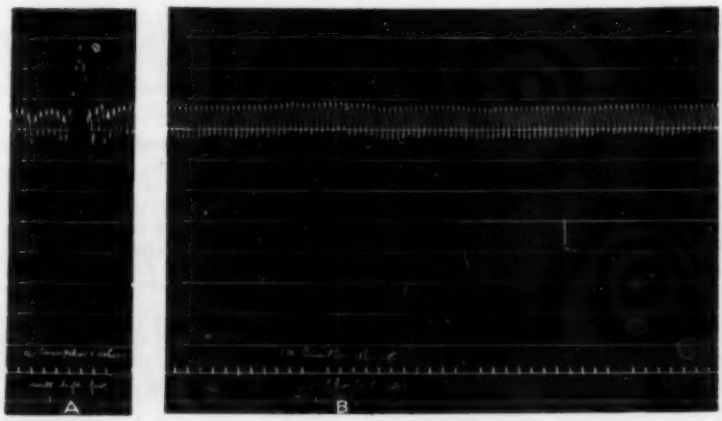


Fig. 3.—Cat decerebrated under ether. At A, 1 c.c. of camphor and ether (10 per cent.) was injected into a pad of the left foot; nerve supply intact. At B, 1 c.c. of camphor and ether (10 per cent.) was injected into another pad of the left foot; sciatic and anterior crural nerves had been cut.

2. Depression of the Vasomotor Center.—In a number of experiments ether was administered by artificial respiration until decerebrate rigidity disappeared. Under these conditions the subcutaneous administration of volatile irritants failed to cause a rise in blood pressure. The same absence of blood-pressure response to injection of irritants occurred when the vasomotor center was injured by a faulty technic in decerebration.

3. Destruction of the Central Nervous System.—In three experiments the vasomotor center was destroyed by pithing. In these animals the subcutaneous injection always failed to cause a rise in blood pressure. This is well shown in the experiment of April 5, 1916. The cat was decerebrated under ether as usual. The injection of 1 c.c. of oil of turpentine into the center pad of the right foot caused a rise of blood pressure of 18 mm., from 138 mm. to 156 mm (Fig. 1, A). The medulla was then destroyed. Two minutes later the blood pressure was 27 mm. The injection of oil of turpentine into the center pad of the left foot failed to modify the blood pressure in the slightest degree (Fig. 1, B).

4. Intravenous Injections.—Oil of turpentine was injected intravenously in several animals; 1 c.c. of the pure oil caused a prompt fall in blood pressure and usually resulted fatally. Smaller doses almost invariably caused a fall in blood pressure, never a rise. Thus in the experiment of April 3, 1916, 1 c.c. of an official emulsion of oil of turpentine caused the blood pressure to fall from 160 mm. to 80 mm.

That the heart plays little or no part in the rise in blood pressure following the subcutaneous injection of irritants was evident from those experiments in which the heart's movements were recorded by the Cushny myocardiograph. In these experiments neither the systole nor the diastole of the heart was changed; the rate remained practically constant.

EFFECT OF INJECTION OF IRRITANTS IN SEVERE HEMORRHAGE AND COLLAPSE

In just those conditions in which the measures studied are commonly used, they are least effective. In hemorrhage with falling blood pressure the subcutaneous injection of irritants is of little avail in checking the fall.

In the experiment of Dec. 10, 1915, three injections of camphor and ether, 1 c.c. each, into the pads of the feet, increased blood pressure 36, 42 and 42 mm., respectively,. The animal was then bled, with resulting fall of blood pressure from 180 mm. to 100 mm. Camphor and ether injected into the pad of the right hand two minutes later gave no response. Three minutes later a similar injection into the pad of the left hand gave no response. The viscera were then manipulated and the pregnant uterus excised. Camphor and ether, 1 c.c., injected into the pad of the left hand gave no rise of blood pressure.

In shock, induced by evisceration, with exposure of the viscera to cold, severe manipulation and traction on the mesentery, nephrectomy, etc., the irritants have little or no influence in checking fall of blood pressure.

In the experiment of Dec. 29, 1915, the abdomen was opened, the viscera exposed, cold water poured on them and the mesentery stretched. Four minutes after this manipulation general blood pressure fell from 190 mm. to 120 mm. One c.c. of oil of turpentine was injected into the center pad of the right foot. The blood pressure rose 20 mm. Later both kidneys were removed, and manipulation of the liver and diaphragm carried out. The blood pressure rose 40 mm. and then fell 40 mm. Oil of turpentine, 1 c.c., was injected into the second pad of the left hand. Blood pressure rose 3 mm., to 95 mm., then gradually fell to 78 mm. Blood pressure continued to fall, and when it reached 40 mm. oil of turpentine was injected into the second pad of the right hand, with no effect. Another injection into the center pad of the left foot also had no effect. Blood pressure continued to fall, and the animal died five minutes later.

Experiment of Dec. 28, 1916: Several injections of irritants into the pads of feet and hands gave the usual rises in blood pressure. The abdomen was opened, the viscera roughly handled and cold water poured into the abdominal cavity. During these procedures blood pressure fell 70 mm., to 120 mm. Oil of turpentine, 1 c.c., injected into the third pad of the left hand, was followed by slight rise in blood pressure, 7 mm. Five minutes later, oil of turpentine, 1 c.c., injected into the third pad of the right hand produced no effect.

DISCUSSION OF RESULTS

In a series of experiments in which the volatile irritants ordinarily used in clinical work and, in addition, oil of turpentine, were injected into decerebrate animals, no direct action on the circulation could be observed other than threatened or actual collapse when the irritants were administered intravenously. Subcutaneous injections caused a rise of blood pressure only when the reflex arc was anatomically and physiologically intact. Gross destruction of the central nervous system or severance of nerve supply of the part injected annuls the circulatory effect of the measures studied. Deep anesthesis (ether), severe hemorrhage, shock and collapse likewise abolish the blood-pressure-raising effect of volatile irritants. In other words, any measure destroying or profoundly depressing the function of any portion of the involved reflex arc robs the subcutaneous injection of volatile irritants of its blood-pressure-raising effect. Other points of interest are that the response is directly proportional to the irritant character of the substance administered and to the sensibility of the area injected.

That the rise in blood pressure following the subcutaneous administration of the volatile irritants is entirely reflex in character is a conclusion that in our opinion cannot be escaped.

The effect on blood pressure of the hypodermic administration of irritants, when the reflex arc is intact, is not great. When one takes into account the fact that the animals were made more than ordinarily irritable by decerebration, the blood pressure changes one might expect in animals with normal reflex irritability are very slight indeed, although in the event of retained sensibility the intense pain of an irritant might well modify the results. The transience of the circulatory effect of the irritant injections is important, the average duration of the rise being seconds. The blood pressure curve following these injections resembles that produced by pinching a sensitive part of the body surface, and is, in our judgment, but a sequel of a not very different local trauma. A series of irritant injections is generally followed by a fall in the average level of blood pressure. It is impossible to know whether or not such a fall is due to repeated bombardment of the central nervous system by painful afferent impulses, or to the toxic action of the substances used, or to other conditions of the experiment. It is impossible to produce traumatic shock by the subcutaneous injection of irritants, because of the early development of systemic toxic effects.

The bearing of the results of this study on the ordinary clinical use of the irritants is obvious. In circulatory deficiencies, the result of traumatic or toxic insult to the central nervous system, an irritant injection may fairly be called an added burden and may well accelerate oncoming shock. It is not claimed that the injection of irritants has no

place in clinical work. In conditions in which cutaneous sensibility is present and reflex irritability preserved, an irritant injection may rouse flagging energies for a momentary emergency. It is, however, a two-edged sword and may also be the final instrument of a collapse. The use of such a measure to stimulate an anesthetized or profoundly prostrated or unconscious patient has no experimental justification.

CONCLUSIONS

The volatile irritants are not direct vasomotor stimulants. They act reflexly through irritation of sensory nerve-endings.

Their effect on blood pressure is both slight and transient.

In conditions of abolished reflex irritability, as anesthesia, shock, etc., the volatile irritants are without effect on the blood pressure.

Their clinical value is questionable.

437 West Fifty-Ninth Street.—49 East Fifty-Third Street.

MAY 21 1917
UNIV. OF MICH. LIBRARY

VOLUME 19 IN TWO PARTS—PART II NUMBER 5

THE ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston
THEO. C. JANEWAY, Baltimore
GEORGE BLUE, St. Louis
WARFIELD T. LONGCOPE, New York
W. S. THAYER, Baltimore

MAY 15, 1917

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879

CONTENTS OF VOLUME XIX

JANUARY, 1917. NUMBER 1

PAGE

THE CLINICAL VALUE OF AMBARD'S COEFFICIENT OF UREA EXCRETION. D. SLATER LEWIS, M.D., BALTIMORE 1

THE ACTION OF THE SEVERAL "FEMALE REMEDIES" ON STRIPS OF THE EXCISED HUMAN UTERUS. J. D. PULCHER, M.D., OMAHA 53

THE PRESENT SIGNIFICANCE OF THE AMINO-ACIDS IN PHYSIOLOGY AND PATHOLOGY. DONALD D. VAN SLYKE, PH.D., NEW YORK 56

PROGRESSIVE MUSCULAR DYSTROPHY AS AN ENDOCRINE DISEASE. WALTER TIMME, M.D., NEW YORK 79

BLOOD CHANGES IN ALBINO RATS FOLLOWING REMOVAL OF THE SPLEEN. C. C. WOLFERTH, M.D., PHILADELPHIA 105

EXPERIMENTS ON THE ORIGIN AND CONDUCTION OF THE CARDIAC IMPULSE. VII. SINOVENTRICULAR AND SINO-AURICULAR HEART-BLOCK. J. A. E. EYSTER, M.D., AND WALTER J. MEEK, PH.D., MADISON, WIS. 117

THE OCCURRENCE OF NUCLEAR CHANGES IN THE RED BLOOD CELLS FOLLOWING SPLENECTOMY. QUINTER O. GILBERT, M.D., ANN ARBOR, MICH. ... 149

THE EFFECT OF HEAT AND CONTINUOUS INCANDESCENT ELECTRIC LIGHT IN EXPERIMENTAL ARTHRITIS. WALTER E. SIEMONDS, M.D., AND J. J. MOORE, M.S., M.D., CHICAGO 153

FURTHER QUANTITATIVE STUDY OF THE DUODENAL BLOOD-DERIVED PIGMENTS. J. P. SCHNEIDER, M.D., MINNEAPOLIS 156

FEBRUARY, 1917. NUMBER 2

PAGE

OSTEOGENESIS IMPERFECTA. JULIUS H. HESS, M.D., CHICAGO 163

HEREDITARY HEMORRHAGIC TELANGIECTASIA, WITH REPORT OF THREE FAMILIES AND A REVIEW OF THOSE PREVIOUSLY RECORDED. WALTER R. STEINER, M.D., HARTFORD, CONN. 194

A CLINICAL STUDY OF THE SECRETIONS ON THE PROXIMAL AND DISTAL SIDES OF THE PYLORUS. A. S. ROBINSON, M.D., CLEVELAND 220

THE RELATION OF HYPERTROPHIC OSTEO-ARTHROPATHY TO PULMONARY TUBERCULOSIS. LEO KESSEL, M.D., NEW YORK 239

TYPHOGEN QUOTIENTS. AN ANALYSIS OF THE FACTORS OF UNCERTAINTY IN THE CUTANEOUS TYPHOGEN TEST. EUGENE S. KILGORE, SAN FRANCISCO 263

A COMPARISON OF TWO METHODS OF VACCINATING AGAINST TYPHOID FEVER. EUGENE S. KILGORE, SAN FRANCISCO 276

THE AGGLUTININS AND COMPLEMENT-FIXING ANTIBODIES IN THE SERUM OF PERSONS VACCINATED AGAINST TYPHOID FEVER. K. F. MEYER AND EUGENE S. KILGORE, SAN FRANCISCO 293

d-GLUCOSE TOLERANCE IN HEALTH AND DISEASE. RUSSELL M. WILDER, M.D., AND W. D. SANSUM, M.D., CHICAGO 311

The Archives of Internal Medicine

VOL. XIX. MAY, 1917.—IN TWO PARTS. PART II. No. 5

CLINICAL CALORIMETRY

NINETEENTH PAPER *

THE BASAL METABOLISM OF OLD MEN *

JOSEPH C. AUB, M.D., AND EUGENE F. DU BOIS, M.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM
NEW YORK

The question of the basal metabolism at various ages has been discussed in Paper 12 of this series, and the references to the literature have already been published. It was apparent that our knowledge of the energy exchanges in old age depended almost entirely on the careful work of Magnus-Levy and Falk[1] who studied five old men and seven old women. These results were used by us in drawing the curves which indicated the average level of metabolism at various ages, but it was apparent that after the age of 43 the points on the chart were scanty. This present work is an attempt to fill in the gap.

An effort was made to find men 90 to 100 years old, but it was impossible to obtain suitable subjects. The age limits were then reduced to between 75 and 85 years, and, after much labor, six men were obtained who fulfilled the requirements. They were either inmates of the New York City Home for Aged and Infirm on Blackwell's Island, or men from other institutions about to be transferred to this home. They were all in good condition and fairly well nourished, though on plain and somewhat scanty diets. Considering their ages, they were in good health, though most of them suffered from arteriosclerosis, chronic interstitial nephritis and emphysema, which "normally" accompany advanced years. They were about as active as most persons of their time of life, none of them being engaged in regular work.

The men were selected by one of the writers from the somewhat limited number over 75 years of age who were in the City Home or Municipal Lodging House. Only those in fair health, with clear and apparently reliable histories as to their ages, were chosen, and an effort

* Submitted for publication Dec. 19, 1916.

* Clinical Calorimetry, Eighteenth Paper, The Number of Places of Significant Figures in the Data of Metabolism Experiments, by Gephart, Du Bois and Lusk was published in the Journal of Biological Chemistry, 1916, **27**, 217.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

1. Magnus-Levy and Falk: Der Lungengaswechsel des Menschen in verschiedenen Alterstufen, Arch. Anat. u. Physiol., 1899, Suppl., p. 315.

was made to pick out men who would cooperate in the experimental procedure. Most of them were delighted with the change of food and scene when they were taken from the almshouse to the metabolism ward. All the experiments were made in the morning, the men being placed in the calorimeter with no breakfast except a cup of "caffein-free" coffee. The old men were about as quiet as the younger controls, with the exception of one whose test had to be repeated.

CASE HISTORIES

CASE 1.—*History.*—Andrew O'C., 77 years old, formerly a car driver, now an inmate of City Home. As a young man he served in the army at the outbreak of the Civil War. He says that he has never been sick, except two years ago, when he was in the hospital for two months with fever. The hair in the axillae has always been scant and he has never had any hair on his thorax. During most of his life he drank about a pint of whisky a day but has had none for six months. He has had no libido for seven or eight years. Recently he has been spending his winters in the City Home and his summers at work. He feels perfectly well and gives no symptoms except frequency of urination at night.

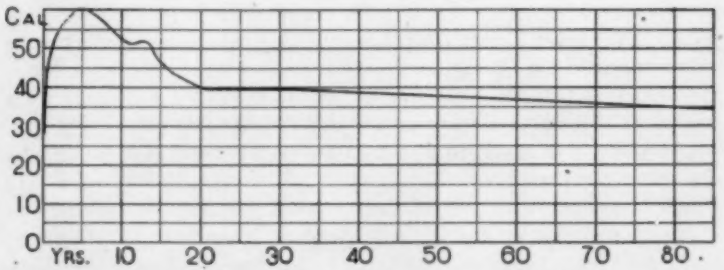


Fig. 1.—Curve showing the level of metabolism at different ages. Results are expressed in terms of calories per hour per square meter of surface area (Linear and Height-Weight Formulas). In accordance with the findings in the present series, the line is somewhat higher in old age than in the curves published in previous papers.

Physical Examination.—A well nourished man, with white hair and slightly wrinkled skin, who looks about 65 years old. No arcus senilis. Heart sounds are of good quality, with an occasional premature systole. There is a faint blowing systolic murmur at the apex. Blood pressure: 235 mm. systolic; 100 mm. diastolic. The pubic hair is scant and of feminine type. Genitalia normal.

The man was of active disposition and spent most of his time walking about the ward. He was the least senile of the group.

CASE 2.—*History.*—Henry L., 78 years old, formerly a baker, now an inmate of City Home. Six years ago he broke his leg and was in the hospital five months. He passes urine twice at night. He has used alcohol sparingly, but has taken a great deal of snuff.

Physical Examination.—Well nourished, skin wrinkled, looks his full age. There is a slight tremor of the hands. Thorax deep, breath sounds emphysematous, with fine râles at the bases. The left border of the heart percusses

13 cm from the median line. There are a few premature systoles; no murmurs. The radial walls are not palpable. Blood pressure: 155 mm. systolic; 80 mm. diastolic.

His disposition was quiet and he spent most of his time in the hospital sitting in a chair. The first time he was in the calorimeter, March 13, he did not understand the instructions and was very restless, taking snuff, coughing, sneezing and moving about. The second time he was in the calorimeter, March 18, he was quiet and the observation was satisfactory.

CASE 3.—*History.*—Charles H., 79 years old, formerly a cigar maker, now in City Home. Ten brothers and sisters lived to be over 70 years of age. Two years ago he had pneumonia. He passes urine two or three times at night. He has been a moderate drinker of beer and a heavy smoker. No libido for the past five years. He feels perfectly well except for a slight cough in the morning.

Physical Examination.—Rather thin, skin flabby and much wrinkled; well preserved for his age. Thorax deep; breath sounds emphysematous. Left border of cardiac dulness 15 cm. from median line. Blood pressure: 210 mm. systolic; 100 mm. diastolic. Urine contains trace of albumin.

His disposition was active and restless and he spent most of his time standing about the ward or working.

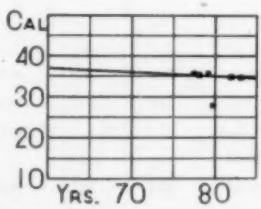


Fig. 2.—Part of Figure 1 with dots representing the findings in the old men of this series.

CASE 4.—*History.*—Charles W., 80 years old, formerly a waiter, for the last year and a half an inmate of City Home. Two years ago his arm was injured in an accident. He was formerly very alcoholic. Fifty-five years ago he had lues. No libido for seven years.

Physical Examination.—Well nourished, skin wrinkled, left border of cardiac dulness 14 cm. to left of median line. At the apex there is a faint systolic murmur. Blood pressure: 180 mm. systolic; 80 mm. diastolic. Breath sounds are emphysematous, with coarse râles at the bases. The urine is normal. Wassermann reaction negative.

This was the most senile of the group. All day long he sat motionless in his chair, taking but little interest in his surroundings.

CASE 5.—*History.*—William C., 83 years old, formerly a newspaper writer, now waiting to be admitted to the City Home. He has had no alcohol for the last forty years, but has smoked excessively. His health has always been good. One week ago he developed a slight cough.

Physical Examination.—Well nourished, skin wrinkled, hair white. Heart normal except for occasional premature systoles. The breath sounds are emphysematous. His disposition is cheerful and he is fairly active. The urine contained 49 gm. glucose on a carbohydrate intake of 190 gm. daily. He had no acidosis.

CASE 6.—*History.*—John B., 83 years old, formerly a storekeeper, now waiting in Bellevue Hospital until he can find a place in a home for the aged.

TABLE 1.—Old Men. Data of—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Case 1..... (Andrew O'C.)	Prelim.	10:35	.....	.....	.....	.....	.....	.....	.....
5/8/16	1	11:35	22.3	20.0	0.82	34.6	0.502	66.3	78.0
69.7 Kg.	2	12:35	22.5	20.0	0.82	34.0	0.502	66.3	78.0
1.87 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	66.6	.....
Case 2 (Henry L.)	Prelim.	11:43	.....	.....	.....	.....	.....	.....	.....
3/13/16	1	12:43	24.6	22.3	0.81	31.6	0.2865	74.2	75.3
67.9 Kg.	2	1:43	25.1	24.2	0.76	34.6	0.2865	79.8	79.9
1.85 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Henry L.	Prelim.	11:31	.....	.....	.....	.....	.....	.....	.....
3/18/16	1	12:31	22.0	18.0	0.89	19.9	0.291	61.3	62.9
68.9 Kg.	2	1:31	23.8	20.7	0.84	25.0	0.291	69.5	72.7
1.85 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 3 (Chas. H.).	.....	10:26	.....	.....	.....	.....	.....	.....	.....
5/3/16	1	11:16	15.7	14.1	0.81	22.4	0.228	47.2	48.0
52.9 Kg.	2	12:26	23.4	21.2	0.80	32.1	0.228	70.8	70.9
1.66 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 4 (Chas. W.)	Prelim.	10:31	.....	.....	.....	.....	.....	.....	.....
5/4/16	1	11:31	17.3	15.4	0.82	27.5	0.228	51.5	60.4
69.1 Kg.	2	12:31	16.9	15.0	0.82	25.5	0.228	50.2	59.8
1.82 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 5 (Wm. C.)..	Prelim.	11:29	.....	.....	.....	.....	.....	.....	.....
3/2/16	1	12:29	20.0	17.0	0.86	22.6	Lost	57.3*	57.4
62.9 Kg.	2	1:30	21.7	18.1	0.87	24.4	Lost	61.5*	65.7
1.68 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 6 (John B.)..	Prelim.	11:55	.....	.....	.....	.....	.....	.....	.....
11/4/15	1	12:55	16.7	15.5	0.78	21.7	0.268†	51.2	51.4
50.5 Kg.	2	1:55	16.4	15.8	0.76	21.8	0.268†	52.1	54.3
1.48 Sq. M.	Aver.	.....	.....	.....	.....	.....	.....	.....	.....

* Calculated from table of Magnus-Levy, assuming 15 per cent. of calories from protein.
† Calculated from 24-hour specimen.

—Calorimeter Experiments

Direct Calorimetry, Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Lin.)	
.....	37.2	....	.....	.....	..	..	..	....	....	Basal; in bed
69.0	37.1	61	14	0.80	..	..	..	....	....	Very quiet
74.4	36.9	59	11	0.82	..	..	..	....	....	Very quiet
.....	.....	....	.....	.....	22	50	28	0.95	35.6	
.....	37.2	69	.....	.....	..	..	..	....	....	In bed; 18 hours after food
70.1	37.1	69	34	0.81	..	..	..	....	....	Restless, coughing
80.4	37.2	66	34	0.75	..	..	..	....	....	Restless, coughing
.....	.....	....	.....	.....	10	68	22	1.13	41.6	(observation not included in averages)
.....	37.1	74	.....	.....	..	..	..	....	....	Basal; in bed
56.7	36.9	70	7	0.90	..	..	..	....	....	Very quiet
69.4	36.9	70	30	0.84	..	..	..	....	....	Quiet
.....	.....	....	.....	.....	12	39	49	0.95	35.5	
.....	37.4	....	.....	.....	..	..	..	....	....	Basal; in bed
42.7	37.3	72	16	0.81	..	..	..	....	....	Very quiet; 50 min. period
72.0	37.4	74	47	0.80	..	..	..	....	....	Fairly quiet; 70 min. period
.....	.....	....	.....	.....	11	60	29	1.12	35.6	
.....	37.0	....	.....	.....	..	..	..	....	....	Basal; in bed
49.2	36.8	55	4	0.82	12	54	34	....	....	Motionless
56.1	36.7	55	7	0.82	12	65	23	....	....	Almost motionless
.....	.....	....	.....	.....	..	..	..	0.74	27.9	
.....	36.7									
55.1	36.7	66	6	.....	..	..	..	....	....	Very quiet; dozed 45 minutes
66.0	36.7	63	18	.....	..	..	..	....	....	Quiet; awake
.....	.....	....	.....	.....	..	..	..	0.94	34.2	
.....	36.8	....	.....	.....	..	..	..	....	....	Basal; in bed
45.7	36.7	49	28—	0.78	14	64	22	....	....	Fairly quiet
52.5	36.7	51	33—	0.75	14	74	12	....	....	Restless last 10 minutes
.....	.....	....	.....	.....	..	..	..	1.02	34.9	

His mother died at the age of 93. The patient himself has always been rather weak physically. Over twenty-five years ago he had malaria and yellow fever, which caused deafness in the right ear. Ten years ago he discovered that his right eye was almost blind. For the last two or three years his memory has been failing, particularly for recent events. He has been a heavy smoker and when young was moderately alcoholic. At present he has marked nocturia. He kept at his clerical work until July, 1915.

Physical Examination.—Well preserved old man, skin only slightly wrinkled, moderate flabbiness of flesh, slight tremor of hands, gait shuffling. The right eye shows a cataract. The heart is slightly enlarged, with an occasional premature systole. There is a faint systolic murmur at the apex and a rough diastolic murmur. Radials are faintly palpable. The lungs are emphysematous. Blood pressure: systolic, 180 mm.; diastolic, 100 mm. Temperature normal; pulse, 55 to 75.

This patient was becoming senile rather rapidly. At the time of the calorimeter observation he was fairly active and spent some of his time walking about the ward. A month or so later he was almost blind, failing mentally and glad to stay in his chair all day.

DISCUSSION OF RESULTS

The calorimeter findings on the group of old men can be compared directly with the findings on Boy Scouts and normal adults between the ages of 20 and 47. The experimental methods used with all of these subjects were the same in almost all particulars. There was, however, one difference between the groups which could not be avoided. The younger subjects were active men on liberal diets, and almost all of them came to the calorimeter room from their homes on the mornings of the experiments. The old men were beyond the working age, they had been on rather meager fare, and they were all kept in the metabolism ward for several days before the tests were made. All of these factors tend to decrease the total metabolism in the same manner in which cage life affects a dog.[2] Still they are part and parcel of old age. It would be difficult to find hard working men of 80 on large diets, or normal men in the prime of life leading the existence of octogenarians.

If we look at the results of the calorimeter experiments we are struck by their uniformity in five of the observations. The first experiment on Henry L. is published for the sake of completeness, but it cannot be considered a test of the basal metabolism. The old man was stupid and did not understand the instructions to stay quiet. He turned frequently from side to side and inhaled snuff which he had smuggled into the calorimeter. This made him cough and sneeze. The second time he was in the calorimeter he was quiet and the observation was very satisfactory. It will be noted that the metabolism of Charles W. was unusually low. This may be accounted for by the fact that he was much more senile than the others. While this finding is of

2. Lusk, G.: Animal Calorimetry, Paper 11, Jour. Biol. Chem., 1915, **20,** 565; and Allen and Du Bois: Clinical Calorimetry, Paper 17, THE ARCHIVES INT. MED., 1916. **17,** 1056.

TABLE 2.—Old Men. Clinical Data[1]

Case Number Name and Date	Food			Food N., Gm.	Urine N., Gm.	Feces N., Gm.	Excreta N.,[2] Gm.	Nitrogen Balance, Gm.	Body Wt., Kg.	Urine Volume, C.c.	Calories per Kg.	Blood Pressure
	Total Calories	Carbohyd., Gm.	Fat, Gm.									
Case 1 Andrew O'C.												
5/ 7/16	2,254	228	125	10.7	9.1	1.1	10.1	+0.6	....	1,100		
5/ 8/16	2,524	240	135	11.2	9.5	1.1	10.6	+0.6	....	1,675		
5/ 9/16	2,502	278	136	7.2	9.4	0.7	10.1	−2.9	70.2	1,420	37	
5/10/16	2,443	277	130	4.0	7.2	0.4	7.6	−3.6	....	1,760	..	235–100
5/11/16	3,043	445	120	4.0	7.2	0.4	7.6	−3.6	70.2	1,520	29	
5/12/16	3,043	436	125	4.1	4.0	0.4	4.4	−0.4	70.1	1,440	29	
Case 2 Henry L.												
3/10/16	2,766	286	129	15.4	8.8[3]	1.5	10.3	+5.1	....	1,500[3]		
3/11/16	2,885	310	135	18.9	8.2	1.4	9.5	+4.4	69.1	760	42	
3/12/16	2,824	304	129	15.0	9.0[4]	1.5	10.5	+4.5	69.1	1,080[4]	41	
3/13/16	.....	...	...	....	6.1[5]	...	....	.....	67.9	1,087[5]	..	154–80
3/14/16	2,924	323	131	14.7	7.2	1.5	8.7	+6.0	68.7	580	41	
3/15/16	3,511	353	180	14.3	7.5	1.4	8.9	+5.4	69.1	650	50	
3/16/16	3,577	352	186	15.6	10.4	1.6	11.9	+3.7	69.6	960	51	
3/17/16	3,400	336	186	15.4	7.1	1.5	8.6	+6.8	69.5	600	50	
3/18/16	.....	...	...	....	...	...	....	.....	....	.....	..	153–100
Case 3 Charles H.												
5/3/16	1,954	184	101	10.2	7.4	1.0	8.4	+1.8	52.9	1,045	..	210–100
5/4/16	2,299	218	121	11.0	8.2	1.1	9.3	+1.7	53.6	800	43	
Case 4 Charles W.												
5/3/16	2,008	220	92	9.8	6.4	1.0	7.4	+2.4	....	1,480		
5/4/16	1,765	153	97	9.1	7.0	0.9	7.9	+1.2	69.1	1,660	..	180–100
Case 5 William C.												
3/2/16	1,825[7]	191[6]	82	11.0	11.3	...	....	.....	62.9	1,940[6]	29	
Case 6 John B.												
11/ 4/15	1,364	126	69	7.9	6.6	...	....	.....	50.5	1,230	27	Syst. 180–100 Diast. 100
12/12/15	1,450	195	60	3.4								
12/13/16	1,326	189	51	3.2	4.1	...	....	.....	51.0	700		

1. Temperature normal in all cases throughout the experiments.
2. Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.
3. Twenty-three hours fifteen minutes.
4. Twenty-three hours thirty minutes.
5. Twenty-three hours thirty minutes.
6. 48.7 gm. glucose in urine.
7. Approximately.

importance in showing the great depression in metabolism which may occur in old age, we are not justified in using it to obtain the average figure which represents the heat production of men of his age. The average for the other five men was 35.1 calories per square meter per hour, and the average deviation from this mean was a little over 1 per cent. When we take the group of fifteen younger men studied in the calorimeter, we find an average deviation from the mean of about 3 per cent. The results on Charles W. show a deviation of 21 per cent. from the average of the other old men. He is therefore excluded from the averages as the result of the rule which debars an observation in which the deviation from the mean is greater than four times the average deviation.

TABLE 3.—Old Men. Summary

Case Number and Name	Age, Yrs.	Weight, Kg.	Height, Cm.	Signs of Senility	Surface Area (Lin.) Sq. M.	Total Calories in 2 Hours		Cal. per Hour		Per Cent. from Adult, Av. 39.7	Av. R. Q.	Av. Pulse
						Indirect	Direct	Per Kg.	Per Sq. M.			
1. Andrew O'C.	77	69.7	171	+ •	1.87	132.3	143.4	0.962	35.6	—10	0.81	59
2. Henry L.	78	67.9	167	++	1.85	154.0	150.5	1.13	(41.6)*	(+ 5)*	0.78	68
Henry L.	..	68.9	...	....	1.85	130.7	126.1	0.949	35.3	—11	0.68	71
3. Charles H. ..	79	52.9	163	+	1.66	118.0	114.6	1.12	35.6	—10	0.89	73
4. Charles W. ..	80	69.1	164	+++	1.82	101.7	105.3	0.736	27.9†	—30†	0.82	55
5. William C. ..	82	62.9	168	++	1.73	118.8	121.2	0.944	34.3	—14	0.86	65
6. John B.	83	50.5	158	+++	1.48	101.3	98.2	1.02	34.9	—12	0.77	59
Total or aver.	..	....	...	....	.....	859.8	859.3	.....	35.1	....	0.81	

* Excluded from averages on account of restlessness.
† Excluded from averages on account of unusually low metabolism.

The average heat production of the five men between the ages of 77 and 83 was 35.1 calories per square meter per hour, which is about 12 per cent. below the average for men between the ages of 20 and 50. This depression in old age is about 7 per cent. less than had been assumed by one of us in a curve based on results obtained by other investigators.[3] As one might expect, the depression of metabolism is somewhat proportional to the degree of senility.

The respiratory quotients lie between the figures 77 and 86, the average being 81. The method of direct calorimetry gives a total of 859.3 calories for the seven experiments, which is within 0.1 per cent. of the total obtained by the independent method of indirect calorimetry (859.8 calories). This agreement is unusually close for two-hour experiments.

3. Du Bois, E. F.: The Respiration Calorimeter in Clinical Medicine, Am. Jour. Med. Sc., 1916, **151**, 781.

SUMMARY AND CONCLUSIONS

A group of six men between the ages of 77 and 83 were studied in the calorimeter. Their average basal heat production was 35.1 calories per square meter per hour, which is 12 per cent. below the average for men between the ages of 20 and 50. The methods of direct and indirect calorimetry agreed closely and the respiratory quotients were all within normal limits.

NOTE.—At the suggestion of Drs. Means and Boothby, a set of normal standards for various ages has been calculated from the age curve published in this paper and Lusk's "Science of Nutrition," third edition, 1917. These will be used in the Sage publications after the present series, until changes in the curve are made by the addition of new data. The figures for females are calculated as 7 per cent. below the average for males, more data, however, being desirable to establish for the female sex the general validity of this method of computation.

CALORIES PER SQUARE METER OF BODY SURFACE PER HOUR (HEIGHT-WEIGHT FORMULA)

Age, Years	Males	Females
14-16	46.0	43.0
16-18	43.0	40.0
18-20	41.0	38.0
20-30	39.5	37.0
30-40	39.5	36.5
40-50	38.5	36.0
50-60	37.5	35.0
60-70	36.5	34.0
70-80	35.5	33.0

477 First Avenue.

CLINICAL CALORIMETRY

TWENTIETH PAPER

THE EFFECT OF CAFFEIN ON THE HEAT PRODUCTION*

J. H. MEANS, M.D.,† BOSTON, J. C. AUB, M.D.
AND
E. F. DU BOIS, M.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM
NEW YORK

The object of this research was to determine the effect of a single large dose of caffein on the respiratory metabolism of normal individuals.

The earliest work on the effect of this drug on the gaseous exchange, so far as we have been able to discover, was that of Hoppe[1] in 1857. He found some increase in the carbon dioxid output after taking caffein, but the conditions of his experiments are open to criticism. He was followed two years later by Smith[2] who studied in a masterly way nearly every aspect of respiration, including the effect of tea, coffee, etc. His technic, so far as one can judge from the description, was excellent. His apparatus was of the open circuit type, the subject breathing through a mask and valves. The inspired air went first through a dry meter and the expired air first through a Woulff bottle, containing pumice stone saturated with sulphuric acid, then through a gutta-percha box having a series of compartments in which the air was exposed, over a large surface, to concentrated potassium hydrate. Next, it was passed through a second Woulff bottle with sulphuric acid, the carbon dioxid was determined by the gain in weight of the absorbers, exactly as is done with the modern calorimeter. The total ventilation of the lungs, the evaporation of moisture from the lungs, the respiration rate and pulse rate were the other factors studied. The oxygen, of course, was not obtained. After taking from 50 to 100 grains of black or green tea leaves, or half an ounce of strong coffee, a rise in the carbon dioxid output was invariably found with

* Submitted for publication Dec. 19, 1916.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

† Henry P. Walcott Fellow in Clinical Medicine, Harvard University.

1. Hoppe: Ueber die Wirkungen des Coffein, Deutsch. Klin., 1857, **9**, 181.

2. Smith, Edward: Experimental Inquiries Into the Chemical and Other Phenomena of Respiration and Their Modifications by Various Physical Agencies, Philosophical Transactions, London, 1859, **149**, 681.

several normal subjects. A very large number of experiments were performed. The rise was anywhere from 15 to 30 per cent. and the maximum usually occurred within an hour from the time of taking the drug. An increase in the ventilation of the lungs of similar proportion was also found. The respiratory rate was sometimes increased, sometimes decreased. The pulse was usually slightly accelerated.

The next extensive study of the effect of caffein on the metabolism, so far as we are aware, is that of Reichert[3] in 1890. This observer worked with dogs, his apparatus being a simple type of water calorimeter. The method of direct calorimetry alone was used. His work may be subject to some criticism, for the dogs were tied down and occasionally struggled. The results of his normal control experiments sometimes differed rather widely, but the faults were remedied to some extent by the very large number of experiments made. The caffein was given subcutaneously. A basal hour was secured first and the dogs were then observed for five hours after receiving the drug. Three series of experiments were performed. In the first series the dose was 0.035 gm. per kg. Five experiments were made. The average increase in heat production was 38.6 per cent. Heat elimination was also increased, but in relation to production was inconstant. In three experiments heat elimination was in excess; in the other two it was not. In the second series, 0.07 gm. per kg. were given. The average increase in heat production was 43.6 per cent. The maximum was reached in two experiments during the first hour after administering the drug; in three, during the second hour. In all the experiments of this series, heat production was in excess of elimination during the first hour, and in three, in excess during the subsequent hour. More heat was eliminated than produced during the remaining hours. In the third series, 0.105 gm. per kg. was given. (The lethal dose was from 0.15 to 0.20 gm. per kg.). In this series there was an average increase in heat production of 71.4 per cent. In all the experiments heat production was in excess of elimination in the first hour and in three also in the second hour. In summing up, Reichert says, "These results show beyond possible doubt that caffein increases heat production, and as a corollary, increases destructive tissue metamorphosis."

More recently, Edsall and Means[4] reported experiments on the effect of caffein on two normal men. In one, after 0.324 gm. of caffein

3. Reichert, E. T.: Action of Caffein on Tissue Metamorphosis and Heat Phenomena, New York Med. Jour., 1890, **51**, 456. For a description of his apparatus see Heat Phenomena in Normal Animals, University Med. Mag., Philadelphia, 1890, **2**, 173, 225, 345.

4. Edsall, D. L., and Means, J. H.: Effect of Strychnin, Caffein, Atropin and Camphor on the Respiration and Respiratory Metabolism in Normal Human Subjects, THE ARCHIVES INT. MED., 1914, **14**, 897.

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Case 1..... (E. F. D. B.)	Prelim.	11:32	.....	.....	.....	.....	.....	.....	.....
4/12/16	1	12:32	25.4	22.7	0.81	31.5	0.502	75.5	82.4
76.5 Kg.	2	1:32	24.7	22.7	0.79	32.7	0.502	75.3	82.0
1.94 Sq. M.									
Av. basal.....	.....	.....	.....	.....	.....	.....	.....	75.4	.....
	3	2:32	27.8	25.7	0.79	37.8	0.686	84.7	87.4
	4	3:32	25.6	22.5*	0.79	37.1	0.668	77.5	82.4
Av. after caffein	.....	.....	.....	.....	.....	.....	.....	.....	.....
E. F. D. B.....	Prelim.	11:07	.....	.....	.....	.....	.....	.....	.....
4/25/16	1	12:07	24.4	22.1	0.80	32.3	0.526	73.2	78.9
77.3 Kg.	2	1:07	27.1	Lost	.....	34.7	0.705	83.5†	82.6
1.95 Sq. M.	3	2:07	25.9	Lost	.....	35.7	0.705	78.9†	83.3
	4	3:07	25.8	24.6	0.77	33.8	0.579	80.7	79.5
	5	4:07	26.2	23.7	0.81	34.0	0.579	78.6	81.6
Av. after caffein	.....	.....	.....	.....	.....	.....	.....	80.6	.....
Case 2 (J. H. M.)..	Prelim.	11:36	.....	.....	.....	.....	.....	.....	.....
4/21/16	1	12:36	24.2	21.9	0.80	32.3	0.534	72.8	81.3
75.3 Kg.	2	1:36	25.1	22.1	0.79	34.9	0.534	76.4	87.5
1.89 Sq. M.									
Av. basal.....	.....	.....	.....	.....	.....	.....	.....	74.6	.....
	3	2:36	29.5	26.5	0.81	36.1	0.604	88.1	84.3
	4	3:36	28.9	27.5	0.77	41.2	0.604	89.9	90.0
	5	4:36	31.5	29.9	0.77	42.2	0.618	98.4	89.7
Av. after caffein	.....	.....	.....	.....	.....	.....	.....	92.1	.....
Case 3 (J. C. F.)...	Prelim.	11:39	.....	.....	.....	.....	.....	.....	.....
4/27/16	1	12:39	23.6	21.2	0.81	28.8	0.502	70.4	70.5
64.3 Kg.	2	1:39	25.9	22.7	0.83	28.6	0.502	75.7	77.4
1.75 Sq. M.									
Av. basal.....	.....	.....	.....	.....	.....	.....	.....	73.1	.....
	3‡	2:42	26.3	24.7	0.78	36.9	0.631	81.1	87.0
	4§	3:39	25.9	22.8	0.82	41.7	0.516	76.1	81.8
	5	4:39	26.6	22.3	0.83	34.2	0.414	78.0	76.6
Av. after caffein	.....	.....	.....	.....	.....	.....	.....	78.4	.....
Case 4 (J. C. A.)...	Prelim.	11:10	.....	.....	.....	.....	.....	.....	.....
4/29/16	1	12:10	22.3	19.1	0.85	29.6	0.546	64.9	70.2
60.2 Kg.	2	1:10	22.8	19.2	0.87	29.6	0.546	64.5	72.4
1.64 Sq. M.									
Av. basal.....	.....	.....	.....	.....	.....	.....	.....	64.3	.....
	3	2:10	25.4	21.9	0.84	32.6	0.546	73.4	75.2
	4	3:10	26.4	24.6	0.78	32.4	0.546	81.2	81.6
	5	4:10	22.6	20.2	0.81	32.4	0.546	66.9	73.1
Av. after caffein	.....	.....	.....	.....	.....	.....	.....	73.8	.....

* Small leak found in blower this hour.
† Calculated from CO_2, R. Q. assumed to be 0.79.
‡ 63-minute period.
§ 57-minute period.

—Calorimeter Experiments

Direct Calorimetry Calories	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
.....	36.9	62								
80.8	36.8	56	0	0.82	..	..	..	....	38.9	Basal; very quiet; on right side
81.0	36.8	58	24	0.79	..	..	..	....	38.8	Basal; very quiet; on back
.....	.....	....	.....	.....	18	56	26	0.99	38.8	Caffein, 0.65 gm. at 1:33 p. m.
80.1	36.9	56	22	0.78	22	58	20	....	38.6	Very quiet
81.5	36.9	55	14	0.79	24	55	21	....	40.0	Very quiet
.....	.....	....	.....	.....	..	..	..	....	41.8	
.....	36.9									
71.5	36.8	56	28	0.80	19	54	27	0.95	37.5	Basal; quiet
78.5	36.8	55	30	.....	..	..	..	....	42.8	Caffein, 0.65 gm. at 12:08 p. m.; quiet
86.2	36.9	60	13	.....	..	..	..	....	41.0	Very quiet; on right side
79.8	36.9	55	11	0.76	19	67	14	....	41.4	Very quiet; on back
82.4	37.0	56	21	0.81	20	53	27	....	40.3	Quiet
.....	.....	....	.....	.....	..	..	..	1.04	41.4	
.....	36.9									
71.6	36.7	59	26	0.80	..	..	..	....	38.5	Basal; fairly quiet
83.4	36.7	55	30	0.79	..	..	..	....	40.4	Basal; fairly quiet
.....	.....	....	.....	.....	19	57	24	0.99	39.5	Caffein, 0.65 gm. at 1:27 p. m.
90.4	36.8	57	21	0.81	18	53	29	....	40.6	Fairly quiet
92.6	36.9	62	22	0.76	18	67	15	....	47.5	Fairly quiet
96.5	37.0	77	29	0.76	17	68	15	....	52.0	Fairly quiet
.....	.....	....	.....	.....	18	63	19	....	48.8	
.....	36.3									
71.2	36.3	....	19	0.81	22	30	28	....	40.2	Basal; very quiet
78.9	36.4	....	45	0.84	21	43	36	....	44.3	Fairly quiet; reading
.....	.....	....	.....	.....	22	46	32	1.14	41.7	Caffein, 0.54 gm. at 1:43 p. m.
81.5	36.3	....	33	0.77	23	62	16	....	46.4‡	Very quiet
73.8	36.2	....	33	0.83	17	49	34	....	43.5¶	Very quiet; slept 25 minutes
77.0	36.3	....	32	0.84	14	48	38	....	44.5	Very quiet
.....	.....	....	.....	.....	18	53	29	....	44.8	
.....	36.8									
75.9	36.9	66	18	0.86	..	..	..	....	39.6	Basal; very quiet
73.6	36.7	65	9	0.80	..	..	..	....	39.3	Basal; very quiet
.....	.....	....	.....	.....	..	..	..	1.07	39.1	Caffein, 0.525 gm. at 1:11 p. m.
74.0	36.9	61	21	0.85	..	..	..	....	....	Fairly quiet
80.6	36.9	59	46	0.77	..	..	..	....	42.5	Fairly quiet
67.7	36.8	50	18	0.82	..	..	..	....	40.7	Very quiet
.....	.....	....	.....	.....	23¶	33¶	44¶	1.23	45.0	

¶ Average of whole experiment.

sodium salicylate, given subcutaneously, there was an average rise of 10.6 per cent. in the metabolism, as measured by indirect calorimetry. The maximum of 13.9 per cent. was reached in the first hour. With the other subject there was an average rise of 3 per cent. and a maximum of 5.7 per cent. after 0.39 gm., given in the same way.

Higgins and Means[5] obtained similar results. In one normal subject, after 0.32 gm. of caffein sodium benzoate subcutaneously there was an average rise of 13.8 per cent. in the indirect calorimetry. The maximum rise of 15.4 per cent. occurred within the first hour. In another normal subject, 0.32 gm. of the same drug was given subcutaneously and was followed by an average rise of 4.5 per cent. and a maximum of 7.2 per cent., which occurred during the second hour.

In neither Edsall and Means' nor in Higgins and Means' experiments was there any consistent change in the respiratory quotient after the drug; in other words, the proportion of fat, carbohydrate and protein utilized showed no regular deviation from the normal.

METHODS OF EXPERIMENTS

Five calorimeter experiments on four normal men were carried out in precisely the same way as already described in the preceding papers of this series.[6] The surface area of all the subjects was determined by the so-called "Linear Formula," described in Papers 5, 9 and 10. The calories derived from protein were calculated from specimens voided between the hours of 8 a. m. and 5 p. m.

The caffein was taken in the form of the pure alkaloid dissolved in water. A tumbler containing the caffein dissolved in 300 c.c. of water at room temperature was placed in the calorimeter when the subject entered. After a preliminary period and one or two hours of observation of the subject's normal basal metabolism, he was told to drink the mixture and was allowed to follow it with a little pure water. After the taking of the drug the observation was continued for three hours, except in one experiment, when the third hour was omitted.

The subjects were studied in the morning hours at complete rest, fourteen to eighteen hours after the last meal. They were not allowed to take coffee or tea for the twenty-four hours previous to the test.

The data of all the experiments are given in the accompanying table.

DESCRIPTION OF SUBJECTS OF EXPERIMENTS

CASE 1.—E. F. D. B., man, aged 34, height 178 cm., physician. For history see Fourth Paper of this series. Since last year he has been in good health; has taken very little exercise since September, 1915. Takes one medium-sized

5. Higgins, H. L., and Means, J. H.: Effect of Certain Drugs on the Respiration and Gaseous Metabolism of Normal Human Subjects, Jour. Pharmacol. and Exper. Therap., 1915, **7**, 1.

6. Papers 1 to 8: THE ARCHIVES INT. MED., 1915, **15**, 793-944; Papers 9 to 17: Ibid., 1916, Part 2, **17**, 855-1059.

cup of coffee at breakfast and occasionally tea in the afternoon, or a small cup of coffee after dinner. Is kept awake by coffee or tea taken after 1 p. m. Tobacco, moderate. Alcohol, occasionally in small amounts.

CASE 2.—J. H. M., man, aged 31, height 177 cm., physician. Measles, mumps, scarlet fever and chickenpox in childhood; a bronchopneumonia at 26 and paratyphoid at 28; otherwise, has always enjoyed good health. Takes exercise only spasmodically, but leads a fairly active life.

Takes one cup of coffee in the morning about half the time, a small cup of coffee after dinner about twice a week, one or two cups of tea in the afternoon about four times a week. One demitasse will not keep him awake; a large cup of coffee in the evening will. Tobacco, moderate. Alcohol, occasionally in small amounts.

CASE 3.—J. C. F., man, aged 23, height 178 cm., chemist. Pleurisy and pneumonia at 6; scarlet fever at 13; occasional sore throat. In good health except for slight nasal obstruction. Exercise: walks three to four miles a day.

He takes a cup of coffee at each meal and sometimes a cup late at night without being kept awake. Tobacco, three to five cigars a day. Alcohol, none.

CASE 4.—J. C. A., man, aged 26, height 175.2 cm., physician. Scarlet fever nine years ago; catarrhal jaundice five years ago; in good health since. Leads a sedentary life, buf always takes some exercise.

Takes two cups of coffee a day; no tea. Even large quantities of coffee in the evening neve keep him awake. Tobacco, ten cigarets a day. Alcohol, occasionally in small amounts.

DISCUSSION OF RESULTS

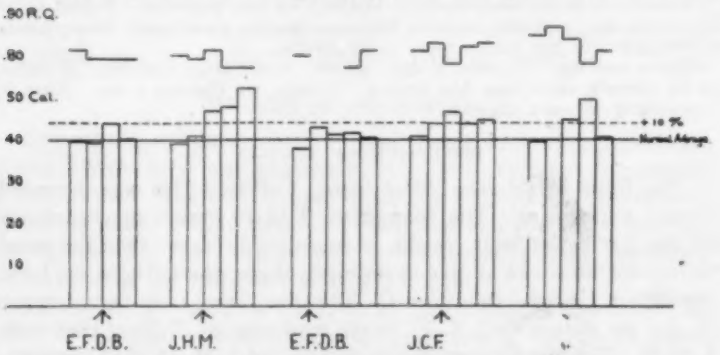
The Basal Metabolism After Giving Caffein.—This was increased in each experiment. The dose given, 8 to 10 grains, approximately 8.6 mg. per kg. of body weight, is considerably larger than the usual therapeutic dose. In all five experiments there was a rise in the basal metabolism (indirect calorimetry). This rise varied from the minimum of 11.3 per cent. with J. C. F., to the maximum of 31.6 per cent. with J. H. M. The highest average rise was that of J. H. M., 23.5 per cent., and the lowest that of J. C. F., of 7.4 per cent. In three experiments, both those on E. F. D. B. and that on J. C. F., the maximum rise occurred in the first hour after receiving the drug. In the experiment on J. C. A., the maximum rise occurred in the second hour, and that in J. H. M. in the third hour. In none of these experiments had the metabolism returned to the basal value when the observation was discontinued. The increments in the metabolism obtained in this series of experiments are definitely greater than those obtained by Edsall and Means and by Higgins and Means when using much smaller doses of the drug. The rises in the basal metabolism of the present experiments are shown graphically in the accompanying figure.

As one looks over the enormous literature on the various actions of caffein, one gets the impression that the numerous contradictory statements are not necessarily due entirely to faulty observation, but possibly because the action of caffein on any given function is extremely variable, often diametrically opposite, in different individuals, and in the same individual with varying dosage. Nevertheless, the present

series of experiments, together with those in the literature, show that an elevation in the basal metabolism is a very frequent action, although its intensity varies considerably in different individuals. In general, there seems to be a larger rise with larger doses.

The Respiratory Quotients.—These show no consistent change in either direction after the drug had been taken.

The Methods of Direct and Indirect Calorimetry. — These agree closely in the hours following the taking of caffein. The total calories as measured by the former method in the hours following the drug were 1,230.3. This is within 1 per cent. of the total of 1,218.0 calories as measured by the method of indirect calorimetry. This agreement of two absolutely independent methods is unusually close, and it confirms the technical accuracy of the findings. The drug had little effect on



Results shown graphically. Columns represent calories per hour as measured by indirect calorimetry. Arrows indicate point at which the caffein was taken. The topmost lines show the respiratory quotients.

the body temperature and the differences between heat elimination and heat production are such as would be found in experiments on normal controls.

The agreement between the methods of direct and indirect calorimetry in the basal hours before the drug was taken is not very close. The direct method gives a total of 687.6 calories; the indirect, 647.8 calories. The method of direct calorimetry is seldom very satisfactory in the first hour of an observation, and these one- or two-hour basal experiments are not long enough to balance up the inequalities. With longer experiments on normal controls the agreement is within a fraction of 1 per cent., as has been shown in previous papers.

The Elimination of Water from Skin and Lungs. — This was increased, after taking the caffein, in every experiment. This was greatest in the case of J. C. F., being 36 per cent. and least in the second

experiment on E. F. D. B., when it was but 5 per cent. The average percentage of calories lost in the vaporization of water during the basal hours was 24.1 per cent.; after taking the caffein the average was 26.3 per cent. The drug affects but slightly the mechanism by which the body dissipates heat in response to an increased heat production.

Nitrogen Elimination.—The total nitrogen in the urine showed a rise after taking caffein in each experiment except that on J. C. A., when the data were not obtained. This rise was greatest in the first experiment on E. F. D. B., 37 per cent., and next greatest in the second experiment on the same subject, 31 per cent. It was least in the case of J. C. F., 6 per cent. J. C. F. likewise had the least rise in basal metabolism, but E. F. D. B. did not have the greatest. This increase might have been merely the washing out of nitrogenous bodies as a result of the caffein diuresis.

The Pulse Rate.—This showed sometimes a slight rise, sometimes a slight fall, or else no change at all after the subject received the drug.

SUMMARY

An increase of from 7 to 23 per cent. in the basal metabolism was found in four normal subjects after receiving 8 to 10 grains of caffein alkaloid (8.6 mg. per kg. of body weight). After taking the drug there was no significant change in the pulse rate, in the respiratory quotient, in the proportions of the various foodstuffs metabolized, or in the percentage of heat lost in the vaporization of water. The independent methods of direct and indirect calorimetry gave results which agreed within 1 per cent.

477 First Avenue.

CLINICAL CALORIMETRY

TWENTY-FIRST PAPER

THE BASAL METABOLISM OF DWARFS AND LEGLESS MEN WITH OBSERVATIONS ON THE SPECIFIC DYNAMIC ACTION OF PROTEIN*

JOSEPH C. AUB, M.D., AND EUGENE F. Du BOIS, M.D.

WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM

NEW YORK

In order to establish more fully the law that the total body metabolism is proportional to the surface area, it is important to establish the law not only for people of normal size and shape, but also for those who are deformed. If the body surface be a true index of the metabolism, and if the body surface be accurately measured, then dwarfs or men with their legs cut off would show proportionally the same basal metabolism per square meter of surface as do normally shaped individuals. But if this relationship holds, is the increase in heat production which follows the ingestion of large quantities of meat the same as in persons of normal shape? It was to try to answer these questions that this series of dwarfs and legless men were studied in the Sage calorimeter at Bellevue Hospital.

THE BASAL METABOLISM OF MEN OF UNUSUAL SHAPE

History.—The basal metabolism of normal individuals has been well established by the large number of normal controls gathered by Benedict, Emmes, Roth and Smith;[1] by Means[2] and by Gephart and Du Bois.[3] The total metabolism of dwarfs has been investigated in one case each by Rubner[4] and by McCrudden and Lusk.[5]

Rubner studied a very small dwarf who was 20 years old and

---

* Submitted for publication Dec. 26, 1916.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

1. Benedict, F. G., Emmes, L. E., Roth, P., and Smith, H. M.: The Basal Gaseous Metabolism of Normal Men and Women, Jour. Biol Chem., 1914, **18,** 139.

2. Means, J. H.: Basal Metabolism and Body Surface, Jour. Biol. Chem., 1915, **21,** 263.

3. Gephart, F. C., and Du Bois, E. F.: The Determinations of the Basal Metabolism of Normal Men and the Effect of Food, THE ARCHIVES INT. MED., 1915, **15,** Part 2, p. 835.

4. Rubner, M.: Biologische Gesetze, Marburg, 1887, p. 10; Beiträge zur Ernährung im Knabenalter, Berlin, 1902, p. 45.

5. McCrudden and Lusk: The Metabolism of a Dwarf, Jour. [illegible]hem., 1912-1913, **13,** 447.

weighed but 6.6 kg., and who "behaved like a fully grown man." His observations were not made under conditions of complete rest, and so are not comparable to our findings. Rubner, however, calculated that the metabolism per square meter, using Meeh's formula, was but slightly higher than that of a breast-fed infant of similar weight. "The larger metabolism of the dwarf," he writes, "is explained by his greater activity, while the infant is very quiet . . . and neither stands nor walks." This showed, according to Rubner, that metabolism was dependent on surface area, not on age.

McCrudden and Lusk's case was in a boy of 17 years, 113 cm. tall and weighing 21.3 kg. By the height-weight chart his surface area is, therefore, 0.8 square meters. He was a patient described by C. A. Herter[6] under the diagnosis of intestinal infantilism. This is a condition in which the arrest of growth is associated with a group of symptoms based on chronic intestinal intoxication. It is associated with fair mental development, marked abdominal distention, moderate anemia, but most strikingly by frequent periods of diarrhea with fatty and putrefying stools. No definite history of this patient is given, but it is one of the cases used by Herter in the description of the syndrome. Practically normal urinary findings on the same case are reported by McCrudden.[7] The patient was studied in a small calorimeter in Dr. Lusk's laboratory, and the routine was practically the same as is now followed in the Sage calorimeter. The results are, therefore, directly comparable to those reported in this paper. Five observations were made on the dwarf, but only one was a true basal experiment, while on the other occasions he had small amounts of food before entering the calorimeter. The one basal observation has been summarized in Table 1, and shows a normal metabolism per square meter of surface area.

In this series we wish to report the metabolism of five dwarfs; two of the achondroplastic type, one rachitic and two with involvement of the glands of internal secretion. Added to this group are two men who had lost both legs. The basal observations in the calorimeter were made in the routine way followed in this laboratory, and fully described in the third and fourth papers of this series.[8] The subjects had had no food for at least fifteen hours, and during the observation remained quietly lying on a bed.

---

6. Herter, C. A.: On Infantilism from Chronic Intestinal Infection, 1908.
7. McCrudden: Chemical Studies on Intestinal Infantilism, Jour. Exper. Med., 1912, **15,** 107. McCrudden and Fales: Ibid., 1912, **15,** 113.
8. Gephart, F. C., and Du Bois, E. F.: The Organization of a Small Metabolism Ward, THE ARCHIVES INT. MED., 1915, **15,** 829. Determination of the Basal Metabolism of Normal Men and the Effect of Food, ibid., p. 834.

We have followed Rischbieth's[9] classification of dwarfs, so careful description of types will not be discussed here. The differentiation of the rachitic, the achondroplastic and the ateliotic (the perfectly proportioned) types is not difficult with the help of the Roentgen ray. However, we have been puzzled in the distinction between the myxedematous and true dwarfism (or ateliotic) types. The skeleton of the ateliotic dwarfs has the same characteristics of bone formation as has the mild cretin, for the cartilage disks of the long bones (according to Rischbieth, and Sternberg[10]) persist throughout life, and the square shaped skull and cretinoid facial appearance may also be present. Both have defective sexual development and both may be mentally defective. Brissaud[11] classifies myxedema, ateliosis and infantilism in one group and Sternberg admits that this is a possible classification. This difficulty in diagnosis confronted us several times in choosing suitable subjects for the investigation.

CASE HISTORIES

CASE 1.—Raphael De P. (Figs. 1 and 2), achondroplastic dwarf, born in Italy, aged 35; a kitchen helper; height 134.7 cm.; weight 40.9 kg.

History.—The family history is negative; no other dwarf in the family for three generations. Had severe illness when a few months old. Since then always well except for chancroid infection twelve years prior to the test. Has been married for eight years to a woman of normal size; has two children, both of normal size.

Physical Examination.—An active, cheerful Italian of normal mentality. The physical examination is negative save for the extremities. All the long bones seem shortened, with slight outward bowing and proportionally large epiphyses. The thighs and upper arms are particularly short. The muscles are powerful. Hands are flat and short, fingers are fat and stubby. Urine, negative. Blood pressure: systolic 120 mm.; diastolic, 90 mm.

CASE 2.—George F.,* hypopituitarism; myxedema; born in Ireland, aged 48; single; a clerk; height 148.8 cm.; weight 53.1 kg.

History.—The family history is negative. He has always been small in stature, though active. For six years he has had occasional attacks of edema, particularly about the eyes, feet and hands. For three years he has had slight shortness of breath and failing vision. He sleeps a great deal and perspires very little. He has had no sexual power for many years.

Physical Examination.—A short, rather fat individual with cretinoid face and feminine type of body. The genitalia are small, the breasts are large. There is no hair except on the head and eyebrows, and this is dry and slightly coarse.

---

9. Rischbieth, H., and Barrington, A.: Dwarfism, Treasury of Human Inheritance, London, 1912, Part VII, Sec. xv A.

10. Sternberg, M.: Vegetationsstörungen und Systemerkrankungen der Knochen, Wien., 1899; Nothnagel's specielle Pathologie und Therapie, Vienna, 1903, **7,** Part 2.

11. Brissaud, E.: De l'infantilisme myxedemateux, Nuov. iconog. de la Salpêtrière, 1897, **10,** 240-282.

* This patient was carefully studied by Dr. W. M. Krause, who reported the case in the Jour. Nerv. and Ment. Dis., 1917, **45,** 193.

The arms are long, the hands of trident type. There was general edema without much pitting on admission, but after a week in the hospital this disappeared, leaving a yellowish, dry, much wrinkled skin. Mentally, he is like a well-behaved child and is always good-natured.

Laboratory Findings.—Blood, normal. Urine occasionally showed small amounts of albumin and rare granular casts; 4,000 c.c. of water intake daily for ten days caused no increase in weight. Phenolsulphonephthalein test, 55 and 63 per cent. in two hours. Wassermann negative. Glucose sugar tolerance,

Figure 1

Figure 2

Fig. 1.—Raphael deP. Achondrodystrophy. The meter stick is opposite the spine.

Fig. 2.—Raphael deP. and a dwarf of ateliotic type.

more than 400 gm. Roentgenogram of hands showed epiphyseal ends of bones to be atrophic. The epiphyseal lines are still visible, particularly the lower ends of the radius and ulna. The head shows a markedly enlarged and somewhat eroded sella turcica.

Case 3.—Samuel G., achondroplastic dwarf, born in Germany, aged 29; single; an actor; height 123.5 cm.; weight 34.9 kg.

History.—The family history is negative. His arms and legs have always been very short for his age. Except for an occasional attack of nausea and vomiting, he is perfectly well. Mentally, he is slow and defective; sexually, he is well developed.

Physical Examination.—Negative, save for the extremities. The torso is of normal shape and size; the arms and legs very short. The head is large and square, with a high forehead and a saddle-shaped nose. The hard palate is high. The extremities are very short, particularly the upper arms and legs, but the muscular development is good. The feet and hands are almost normal size and large for the rest of the extremities. The genitalia are of mature development, the body hair is abundant and of normal masculine distribution. The urine is normal.

CASE 4.—Patrick W. (Figs. 3, 4, 5 and 6), rachitic dwarf, born in United States, aged 38; actor; height 123.8 cm.; weight 37.3 kg.

Fig. 3.—Pat W., rachitic dwarf.

Patient says he was normal until 3 years old when he became moody and his body became distorted. He had walked and talked at the usual age. He has had gonorrhea three times; twelve years prior to the test he had syphilis, followed by very severe nephritis. During this attack he was very edematous and the abdomen was tapped eight times. Since then he has felt perfectly well.

Physical Examination.—A small, misshapen dwarf with marked curvature of the spine and the longer bones. The head appears normal. The chest is very narrow in the upper portion, with a prominent sternum. There is marked flaring of the lower ribs, with Huntington's groove and marked rosary. The spine shows left lateral curvature in the lower thoracic region, with a slight kyphosis. The legs are very short and markedly bent. The feet appear normal.

The arms are short, but the bones are only slightly curved. The epiphyses of all the long bones are large. The genitalia are well developed; the body hair is of masculine type of distribution.

Laboratory Findings.—Urine was negative; specific gravity, 1.025; albumin, negative. Microscopic examination, negative.

CASE 5.—Irwin E., myxedematous dwarf, born in United States, aged 32; actor; height 134 cm.; weight 37.4 kg.

History.—He has always been of small size. At 10 years of age he was short and weighed but 40 pounds. His school work was not very good, as he failed four times in grammar school. He passed for high school when he was

Fig. 4.—Pat W.

15 years old, and stayed there only one year. He is sexually mature, but inactive. The hair on his head has always been soft and plentiful. He perspires freely.

Physical Examination.—He appears like a well developed boy of 14 years. The facies suggests cretinism—thick eyebrows, puffy eyelids, broad nose, wide maxillae, broad jaw and large, widely spaced teeth. There is a pad of fat between the shoulders and a slight degree of adiposity. The hands are short and stubby; the skin slightly dry, but soft and smooth. The genitalia appear normally developed, but the secondary characteristics are scant for there is no hair on the face, in the axillae or on the body, and the pubic hair is of the feminine configuration. The voice is that of male puberty. Otherwise the

physical examination is not remarkable. Blood pressure: systolic, 95 mm.; diastolic 65 mm.

Roentgenogram of head shows a slightly enlarged sella turcica. In the hand there is some hypo-atrophy of the terminal tufts of the phalanges. The epiphyses of the radius and ulna are not united. The epiphyseal lines of the phalanges are clear.

CASE 6.—Harry J. (Fig. 7, described in Paper 9), a legless man, born in the United States, colored, aged 34; beggar. Length is approximately 103 cm., weight 54.6 kg.

Fig. 5.—Pat W. Roentgenogram of knee.

History.—Both legs were cut off by a train when the patient was 6 years old, and since then he has propelled himself on wheels. Seven years prior to the test the right side of the body suddenly became numb and the right arm was completely paralyzed. Slight power returned slowly. He had urethritis seven years previous to the examination, possibly with a chancre, though no secondary manifestations developed.

Physical Examination.—Very muscular negro with short leg stumps. *Face:* Forehead is normal but right side of face is paralyzed; mouth droops and tongue deviates slightly to right. *Chest* is unusually broad and deep, with very powerful muscles in the back, neck and left shoulder and arm. The waist is very narrow; the hips narrow, with poorly developed muscles. The right arm is paralyzed and the muscles are of moderate size but flabby. The

Fig. 6.—Pat W. Spine.

reflexes are exaggerated. The right leg is a very short stump with flabby muscles. The left leg is amputated just above the knee and the stump tapers sharply from the perineal level. The muscles are small and weak. Blood pressure: systolic, 188 mm.; diastolic, 130 mm.

Urine, negative. *Wassermann*, negative.

CASE 7.—Robert L. (described in Paper 9), a legless man, born in the United States, aged 43; beggar; length about 125 cm.; weight 63.8 kg.

Fig. 7.—Harry J.

History.—The patient was a boiler maker for over twenty years and was always healthy and strong. He had syphilis and urethritis nineteen years ago, for which he received treatment for five months. Five years prior to the examination he was hit by a railroad train and both his legs had to be amputated. He now feels well and supports himself by selling pencils. He walks about a mile every day, with crutches.

Physical Examination.—A heavily built, healthy looking man with fat cheeks and prominent abdomen. His chest is large; his arms muscular. The left thigh is cut off just below the level of the perineum. The right leg is cut off just below the level of the knee and the thigh muscles are firm and strong. Otherwise, the patient appears normal, except that over the left lung there are heard many dry, crackling râles, though resonance, tactile fremitus, vocal fremitus and breath sounds are normal.

TABLE 1.—SUMMARY

Case Number and Name	Subject	Age	Height, Cm.	Weight, Kg.	Surface Area, Sq. M. Linear Formula	Calories per Sq. M. per Hour	Variations from Average Normal 39.7 %	Average R. Q.	Total Calories Measured		Divergence of Direct from Indirect, Per Cent.	Average Calories per Hour, Indirect
									Indirect	Direct		
6. Harry J.*	Legless man	35	103±	54.61	1.34	41.3	+4.0	0.80	110.67	106.42	−3.9	55.34
7. Robert L.	Legless man	43	125±	63.81	1.43	41.3	+4.0	0.80	176.90	178.22	+0.7	58.97
4. Patrick W. ...	Rachitic dwarf	38	123.8	37.31	1.20	41.0	+3.0	0.81	98.27	97.74	−0.5	49.17
1. Raphael DeP.	Achondroplasia	35	134.7	40.86	1.24	42.2	+6.3	0.81	104.66	102.20	−2.3	52.33
3. Samuel G.†....	Achondroplasia	29	123.5	34.92	1.06	(48.9)	(+23.0)	(0.82)	(39.56)	(38.26)	−3.3	52.76
5. Irwin E.	Myxedema	32	134.0	37.37	1.17	29.5	−25.7	0.85	68.98	70.31	+1.9	34.49
2. George F.	{Hypopituitary } Hypothyroid	48	148.9	53.05	1.51	31.1	−22.0	0.83	96.57	94.51	−2.1	48.28
J P.‡.....	{ "Intestinal } Infantilism"	17	113.3	21.3	0.8	38.2	−4.0	0.79	61.12			

* Quiet experiment, 5/6/16.
† Forty-five-minute period only. Nauseated. Other observations two hours.
‡ McCrudden and Lusk's case.

DISCUSSION OF RESULTS

Two of the experiments here recorded were technically unsatisfactory and cannot be considered as giving accurate evidence as to the level of the basal metabolism. The achondroplastic dwarf, Samuel G., was nauseated in the calorimeter and the high figures obtained in his brief observation might have been due to the same factor which caused his vomiting. The legless negro, Harry J., was also restless the first time he was in the calorimeter. While he did not move often, his deformity and paralysis of the right arm made each movement a great exertion. In his second experiment he was quiet and the results were satisfactory.

This leaves good determinations of the basal metabolism of seven men of unusual body shape. Five give figures within the normal limits when the results are calculated according to the surface area. These individuals are the two legless men, Harry J. and Robert L., the rachitic dwarf, Patrick W., the achondroplastic dwarf, Raphael de P., and the dwarf, J. P., with intestinal infantilism, described by McCrudden and Lusk. Two dwarfs give results distinctly below the normal. These are Irwin E. and George F., both of whom had many of the characteristics of cretinism, a condition which is always accompanied by a diminution in the heat production.

It therefore seems true that people with abnormal body shape, but with normal glands of internal secretion, have a metabolism which conforms to their surface area. It is therefore possible that the height of metabolism may be a method for differentiating the ateliotic and myxedematous dwarfs.

THE SPECIFIC DYNAMIC ACTION OF PROTEIN

Many investigators have studied the increased heat production which accompanies the metabolism of protein. The literature has been thoroughly reviewed and discussed by Lusk[12] in his book on nutrition, so that only the most important references are given here.

Von Mering and Zuntz[13] believed that the increased metabolism was due to intestinal work following ingestion of food. This was disproved, however, by the fact that fat and carbohydrate increase metabolism far less than an equal quantity of protein. Rubner[14] and Magnus-Levy[15]

12. Lusk, G.: The Elements of the Science of Nutrition, Ed. 3, Philadelphia, 1917.

13. Von Mering and Zuntz, N.: In wiefern beeinflusst Nährungszufuhr die thierischen Oxydationsprocesse, Pflüger's Arch. f. d. ges Physiol., 1877, **15,** 634.

14. Rubner, Max: Die Gesetze des Energieverbrauchs bei Ernährung, Leipzig, 1902.

15. Magnus-Levy, Ad.: Ueber die Grösse des respiratorischen Gaswechsels unter dem Einfluss der Nährungsaufnahme, Pflüger's Arch. f. d. ges. Physiol., 1894, **55,** 1.

fed bones to a dog and obtained but slight increase in metabolism in spite of the intestinal irritation and activity. Rubner[14] believed that this "specific dynamic action" was due to the cleavages and oxidations necessary to make the foodstuffs available for use by the body cells. The heat given off by these preliminary reactions constituted the waste heat of the dynamic action. In the case of protein, part of the heat, he thought, was derived from the carbohydrate portion burned, but chiefly it arose from the chemical reactions of the remainder of the protein molecule, whose end-products appear in the urine, mostly as urea. This energy, he thought, was liberated unused by the organism. Voit[16] believed that the cells of the body were stimulated to a higher metabolism by food being brought to them. Lusk[17] gave amino-acids and glucose to normal and phlorhizinized dogs. The metabolism of the normal dog was stimulated by both foodstuffs, but the phlorhizinized dog had no change in metabolism when glucose was administered and totally excreted. However, the amino-acids, glycocol and alanin, though unoxidized and excreted with all their energy as sugar and urea, still caused an increase of metabolism. The conclusion is clear that it is not the energy contents of the amino-acids themselves, for those were excreted, but, to quote from the original, "that intermediary products, such as glycollic acid or lactic acid, provide the stimulus. These experiments afford conclusive proof of a true chemical stimulation of protoplasm within the mammalian organism, and offer a logical explanation of the specific dynamic action of protein."

It was to find out where this chemical stimulation occurred, whether in the muscles or in the internal organs, that the following experiments were made at the suggestion of Dr. Lusk. Individuals were taken with normal torsos, but a marked variation in the size of their extremities. If the specific dynamic action of a test protein meal were due to the muscle volume or the surface area, then an achondroplastic dwarf and legless man should show a proportionally smaller stimulation of metabolism than did the normal controls. If the action were due to one of the internal organs, the response of all the subjects tested should be approximately the same.

The subjects chosen were a legless man, an achondroplastic dwarf and three normal controls whose weight closely approximated that of the two abnormal cases. The basal metabolism was determined, following the usual routine technic of this laboratory, fifteen to eighteen hours after the last food. Within the next week the subject was prepared as for a basal observation, but in the morning he was given a

16. Voit, C.: Physiologie des Stoffwechsels und der Ehnährung, Leipzig, 1881, p. 308.

17. Lusk, G.: Animal Calorimetry, XI, An Investigation Into the Causes of the Specific Dynamic Action of the Foodstuffs, Jour. Biol. Chem., 1915, **20,** 555.

large protein meal. This consisted in all cases, except that of Louis M., of about 660 gm. of thoroughly scraped lean beefsteak, chopped very fine and cooked only superficially. In each case a sample was analyzed for protein and fat. A small amount of stewed tomatoes and "Kaffee Hag" were allowed in order to make the food more palatable. Louis M., whose observations are taken from the work of Gephart and Du Bois,[18] had been given the same meal with the addition of 100 gm. of fat. When the subject had finished eating he was put in the calorimeter, and two hours after the start of the meal the observation was begun In several cases the metabolism was also determined for a thirty-minute period, starting one and one-half hours after the start of the meal. All of the subjects received approximately the same amount of protein (24 gm. of nitrogen) and the temperature of the calorimeter was the same for all observations, so that the results are directly comparable; for Rubner[14] pointed out that a change in temperature has a marked effect on the specific dynamic action of protein, and Gigon[19] claimed that the dynamic action did not vary directly with the amount of protein ingested.

The urine was collected in hourly periods, when this was possible, and each sample was analyzed separately for nitrogen, and in most observations for sulphur. In this way the speed of the nitrogen and sulphur excretion could be compared with the increase in metabolism (Table 2). The urinary nitrogen was determined by the usual Kjeldahl method and the sulphur by Benedict's method. The amount of protein and fat ingested was calculated from analyses of each sample of steak used.

CASE HISTORIES

CASE 8.—S. K., normal control, born in Japan, aged 33; medical student; height 161.5 cm.; weight 49.5 kg.

The history is entirely negative, except that fifteen years prior to examination he had slight symptoms of beriberi, which rapidly disappeared when he changed his diet. He exercises a great deal, mostly at jiu jutsu and wrestling.

The physical examination is negative. He is a Japanese of very marked muscular development and good physique.

CASE 9.—G. T. B., normal control, born in the United States, aged 25; medical student; height 164.5 cm., weight 54.4 kg.

He has always been fairly well, but never athletic or very strong. His life has been a sedentary one, particularly for some months previous to the test, during which he has been studying for examinations.

The physical examination is negative.

CASE 10.—Louis M.,[20] normal control, born in Germany, aged 22 years; barber; weight 51.7 kg.

A short, thin, normal individual with small frame and muscles.

---

18. Gephart, F. C., and Du Bois, E. F.: Determination of the Basal Metabolism of Normal Men and the Effect of Food, Clinical Calorimetry, Fourth Paper, THE ARCHIVES INT. MED., 1915, **15,** 835.

19. Gigon, Alfred: Ueber den Einfluss der Nahrungsaufnahme auf den Gaswechsel, Arch. f. Physiol., 1911, **140,** 544.

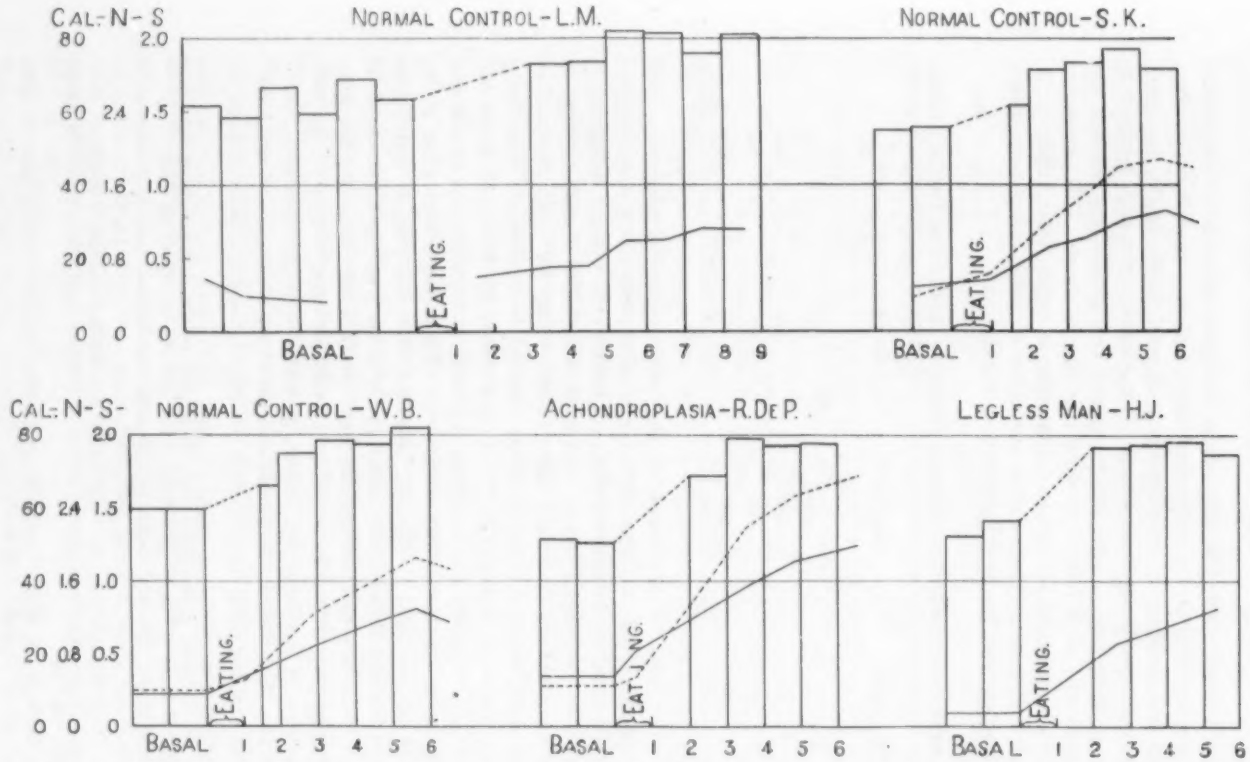

CAL: N - S
NORMAL CONTROL - L.M.
NORMAL CONTROL - S. K.
80 2.0
60 2.4 1.5
40 1.6 1.0
20 0.8 0.5
0 0 0
EATING.
BASAL 1 2 3 4 5 6 7 8 9
BASAL 1 2 3 4 5 6
CAL: N - S -
NORMAL CONTROL - W.B.
ACHONDROPLASIA - R. DE P.
LEGLESS MAN - H.J.
80 2.0
60 2.4 1.5
40 1.6 1.0
20 0.8 0.5
0 0 0
EATING.
BASAL 1 2 3 4 5 6
BASAL 1 2 3 4 5 6
BASAL 1 2 3 4 5 6

Chart 1.—Specific dynamic action of protein. Columns show the basal heat production in calories per hour and the increased metabolism after the subject has eaten chopped beef containing 23 to 25 gm. of nitrogen. The dotted line represents the excretion of sulphur in the urine in decigrams. The continued line gives the nitrogen elimination in grams.

The observations brought out several points of interest. The graphic chart shows that the metabolism had risen to a considerable degree one and one-half hours after the meal, and nearly to the maximum intensity two hours after eating. It remained at the high level for at least seven hours, with the maximum heat production between the fourth and sixth hours following ingestion of food. This shows that the absorption of food from the intestine is rapid, for certainly within one and one-half hours after partaking of food it has been partly absorbed from the bowel and is being metabolized.

TABLE 2.—NITROGEN AND SULPHUR EXCRETION IN THE DOG (AFTER RUBNER)

Period	Sulphur	Nitrogen	$\frac{N}{S}$
0-3	0.448	5.57	12.4
3-9	0.387	8.94	23.1
9-2	0.257	5.32	20.7
2-9	0.131	2.66	20.3

But what is the index of the true protein metabolism? Voit emphasized the fact that the amount of protein eaten was not good evidence of the amount metabolized, but that the urinary nitrogen was a much more direct index. But even though the urinary nitrogen is direct evidence, its hourly value is still rising for some hours after the stimulation of protoplasm has reached its maximum. This same fact has been observed in the study of dogs by Williams, Riche and Lusk,[20] who point out that there is a delay in the excretion of nitrogen following the metabolism of protein. They found that after giving 700 gm. of meat to the dog the maximum increase of metabolism was reached in two hours, but that the urinary nitrogen excretion did not reach its maximum until the sixth hour. There is, during this time, a temporary accumulation of nonprotein nitrogen, largely of the urea portion, in the blood and tissues, as was shown by Folin and Denis[21] and by Miss Wishart.[22] It was also shown by Reilly, Nolan and Lusk[23] that in a dog made diabetic with phlorhizin, the sugar derived from the

20. Williams, Riche and Lusk: Metabolism of the Dog Following the Ingestion of Meat in Large Quantities, Jour. Biol. Chem., 1912, **12,** 349.

21. Folin, Otto, and Denis, W.: Protein Metabolism from the Standpoint of Blood and Tissue Analysis, Jour. Biol. Chem., 1911-1912, **11,** 87.

22. Wishart, Mary: Animal Calorimetry, Paper IX. The Influence of Meat Ingestion on the Amino-Acid Content of Blood and Muscle, Jour. Biol Chem., 1915, **20,** 535.

23. Reilly, F. H., Nolan, F. W., and Lusk, G.: Phlorhizin Diabetes in Dogs, Am. Jour. Physiol., 1898, **1,** 395.

protein was excreted more rapidly than was the nitrogen. This is direct proof of the delayed excretion of nitrogen after its metabolism. Lusk[24] and Csonka[25] have shown that the administration of amino-acids to the phlorhizinized dog causes a maximal rise in both the heat production and sugar elimination in the first one or two hours, which indicates

TABLE 3.—NITROGEN-SULPHUR RATIOS AFTER MEAT INGESTION

Name	Date	Time	Nitrogen per Hour, Gm.	Sulphur per Hour, Mg.	$\frac{N}{S}$	Remarks
R. DeP.	3/15	7:20 a. m. to 1:10 p. m.	0.60	.....	....	Basal
	3/16	5:00 a. m. to 8:55 a. m.	0.57	31.9	17.7	662 gm. meat at 9:00 a. m.
		8:55 a. m. to 9:55 a. m.	0.87	35.3	24.7	
		9:55 a. m. to 12:17 p. m.	1.27	82.6	15.7	
		12:17 p. m. to 1:32 p. m.	1.61	135.6	11.9	
		1:32 p. m. to 3:04 p. m.	1.88	159.7	11.8	
		3:04 p. m. to 4:02 p. m.	2.02	173.0	11.7	
S. K.	5/16	9:27 a. m. to 1:26 p. m.	0.46	22.7	20.2	Basal
	5/18	9:15 a. m. to 11:23 a. m.	0.55	38.8	14.2	660 gm. meat at 8:20 a. m.
		11:23 a. m. to 12:22 p. m.	0.91	74.8	12.2	
		12:22 p. m. to 1:23 p. m.	1.02	94.1	10.9	
		1:23 p. m. to 2:32 p. m.	1.19	111.8	10.1	
		2:32 p. m. to 3:30 p. m.	1.29	117.9	10.9	
		3:30 p. m. to 4:24 p. m.	1.19	111.7	10.6	
W. B.	5/22	8:45 a. m. to 1:02 p. m.	0.87	25.0	14.6	Basal
	5/25	6:55 a. m. to 8:23 a. m.	0.54	32.7	16.6	600 gm. meat at 8:25 a. m.
		8:23 a. m. to 10:29 a. m.	0.61	34.4	17.7	
		10:29 a. m. to 12:30 p. m.	0.92	80.8	11.4	
		12:30 p. m. to 1:30 p. m.	1.12	104.3	10.7	
		1:30 p. m. to 2:28 p. m.	1.22	118.2	10.3	
		2:28 p. m. to 3:29 p. m.	1.13	110.7	10.2	
Harry J.	5/10	5:00 a. m. to 9:46 a. m.	0.36	23.7	14.7	660 gm. meat at 9:00 a. m.
		9:46 a. m. to 1:48 p. m.	0.94	61.1	15.3	
		1:48 p. m. to 3:07 p. m.	1.30	114.5	11.3	

that the rise in heat production approximately parallels the speed of amino-acid metabolism. This is before the period of maximal nitrogen elimination. Then, too, the sulphur portion of the protein is excreted

24. Lusk, G.: Animal Calorimetry, Paper XI. An Investigation Into the Causes of the Specific Dynamic Action of the Foodstuffs, Jour. Biol. Chem., 1915, **20,** 610.

25. Csonka, F. A.: Animal Calorimetry, Paper X. The Rate at Which Ingested Glycocoll and Alanine Are Metabolized, Jour. Biol. Chem., 1915, **20,** 539.

TABLE 4.—DATA OF CALORIMETER—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Case 3 (Saml. G.)..	Prelim.	10:14	.....	.....	.....	.....	.....	.....	.....
3/8/16									
34.9 Kg.	1	10:59	13.4	11.9	0.82	19.2	0.261	39.6	40.2
1.08 Sq. M									
Case 4 (Pat W.)....	Prelim.	11:38	.....	.....	.....	.....	.....	.....	.....
3/24/16									
37.3 Kg.	1	12:38	15.7	13.7	0.83	16.1	0.266	46.0	47.1
1.20 Sq. M.	2	1:38	17.1	15.8	0.79	17.3	0.266	52.3	50.1
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 5 (Erwin E.).	Prelim.	12:05	.....	.....	.....	.....	.....	.....	.....
3/6/16									
37.4 Kg	1	1:05	12.1	10.6	0.83	12.5	0.314	35.3	40.6
1.17 Sq. M.	2	2:05	11.9	10.0	0.86	12.5	0.314	33.7	38.0
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 2 (Geo. F.)....	Prelim.	11:40	.....	.....	.....	.....	.....	.....	.....
1/7/16									
53.1 Kg.	1	12:40	16.4	14.0	0.86	16.5	0.309	47.0	51.8
1.51 Sq. M	2	1:40	16.2	15.0	0.79	16.2	0.309	49.6	50.6
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 8 (S. K.).....	Prelim.	10:50	.....	.....	.....	.....	.....	.....	.....
5/12/16									
50.4 Kg.	1*	11:20	11.5	9.6	0.87	13.0	1.288	31.7	32.5
1.50 Sq. M.	2	12:20	26.1	21.2	0.89	23.2	1.288	70.6	66.5
	3	1:20	25.3	22.1	0.83	27.4	1.288	72.3	71.8
	4†	2:30	23.9	25.9	0.81	35.5	1.288	84.4	80.1
	5‡	3:20	19.7	18.6	0.77	25.4	1.288	59.9	62.5
S. K.	Prelim.	10:56	.....	.....	.....	.....	.....	.....	.....
5/16/16									
49.5 Kg.	1	11:56	18.3	16.5	0.81	28.3	0.457	54.8	61.6
1.50 Sq. M.	2	12:56	17.9	16.9	0.77	26.1	0.457	55.5	61.2
	Aver.	.....	.....	.....	.....	.....	.....	....	.....
Case 7 (Robt. L.)..	Prelim.	11:21	.....	.....	.....	.....	.....	.....	.....
12/9/14									
62.8 Kg.	1	12:21	18.2	16.0	0.83	23.5	0.536	53.0	57.8
1.43 Sq. M.	2	1:21	21.1	19.0	0.81	24.9	0.536	63.0	65.3
(measured)	3	2:21	19.8	18.6	0.77	24.8	0.536	60.9	64.0
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 6 (Harry J.).	Prelim.	11:06	.....	.....	.....	.....	.....	.....	.....
12/11/14									
56.8 Kg.	1	12:06	20.7	18.8	0.80	23.7	0.419	62.5	59.3
1.33 Sq. M.	2	1:06	22.1	18.1	0.89	25.2	0.298	61.6	62.0
	3	2:06	21.9	19.9	0.80	24.5	0.298	66.2	61.3
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....

* 30-minute period. † 70-minute period. ‡ 50-minute period.

—Experiments in Dwarfs and Legless Men

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Lin.)	
.....	36.9	80	.....	.....	..	..	..	....	....	Basal; in bed
38.3	36.9	80	11	0.82	18	49	33	1.51	48.9	Quiet, 45 min. period; at 11:32 became nauseated
.....	36.6	....	.....	.....	..	..	..	....	....	Basal; in bed
46.9	36.6	70	15	0.84	15	48	37	....	....	Asleep 30 minutes; very quiet
50.9	36.6	79	17	0.79	14	63	23	....	....	Awake; quiet
.....	.....	....	.....	.....	15	55	30	1.32	41.0	
.....	37.3	....	.....	.....	..	..	..	....	....	Basal; in bed
35.0	37.2	61	11	0.84	..	..	..	....	....	Very quiet; asleep 30 min.; read 10 min.
35.3	37.1	64	7	0.88	..	..	..	....	....	Quiet; no reading
.....	.....	....	.....	0.86	24	36	40	0.92	29.5	
.....	37.0	....	.....	.....	..	..	..	....	....	Basal; in bed
47.1	36.9	59	15	0.87	17	37	46	....	....	Quiet; dozed
47.4	36.8	59	16	0.79	17	61	22	....	....	Quiet
.....	.....	....	.....	0.83	17	49	34	0.80	31.1	
.....	36.8	....	.....	.....	..	..	..	....	....	9:15 to 10:12, ate 602 gm. beef containing 24.1 gm. N.
29.9	36.7	67	4	0.95	54	8	38	....	....	Very quiet
66.8	36.7	....	12	0.99	48	2	50	....	....	Very quiet
69.5	36.7	69	18	0.86	47	25	28	....	....	Very quiet
88.3	36.7	69	26	0.82	47	32	21	....	....	Quiet
61.4	36.7	65	.....	0.74	48	46	6	....	....	Quiet
.....	36.4	....	.....	.....	..	..	..	....	....	Basal; in bed
53.9	36.2	55	3	0.81	..	..	..	....	....	Very quiet; almost motionless
60.9	36.2	55	9	0.76	..	..	..	....	....	Very quiet; urinated
.....	.....	....	.....	.....	22	57	21	1.11	36.8	
.....	36.9	....	.....	.....	..	..	..	....	....	Basal
51.7	36.8	78	8	0.84	27	40	33	....	....	Asleep
63.2	36.8	72	22	0.81	23	50	27	....	....	Fairly quiet
68.4	36.8	73	19	0.76	23	62	15	....	....	Fairly quiet
.....	.....	....	.....	.....	..	..	..	....	41.3	
.....	36.8	....	.....	.....	..	..	..	....	....	"Basal"
53.4	36.7	64	13	0.80	18	56	26	1.12	....	Restless
62.0	36.7	65	16	0.91	13	27	60	1.10	....	Restless
62.2	36.8	62	13	0.80	12	60	28	1.19	....	Restless

TABLE 4.—Data of Calorimeter Experiments—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Harry J. ..... 5/5/16 54.6 Kg. 1.34 Sq. M.	Prelim.	10:30	.....	.....	.....	.....	.....	.....	.....
	1	11:30	17.8	15.9	0.82	25.6	0.210	53.1	54.2
	2	12:30	18.5	17.4	0.79	24.9	0.210	57.5	55.0
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Harry J. ..... 5/10/16 55.8 Kg. 1.34 Sq. M.	Prelim.	11:00	.....	.....	.....	.....	.....	.....	.....
	1	12:00	26.2	23.9	0.80	28.9	1.296	77.9	69.3
	2	1:00	27.1	23.9	0.83	32.7	1.296	78.2	74.8
	3	2:00	27.3	24.0	0.84	40.6	1.296	78.9	81.2
	4	3:00	20.3	23.1	0.80	43.9	1.296	75.6	80.3
Case 1..... (Raphael DeP.) 3/15/16 46.9 Kg. 1.24 Sq. M.	Prelim.	11:02	.....	.....	.....	.....	.....	.....	.....
	1‖	12:05	18.9	16.8	0.82	22.5	0.606	52.8¶	54.0
	2‖	1:02	16.6	15.0	0.81	20.8	0.602	51.9¶	50.6
	3	.....	.....	.....	.....	.....	.....	.....	.....
Raphael DeP. ..... 3/16/16 46.9 Kg. 1.24 Sq. M.	Prelim.	11:02	.....	.....	.....	.....	.....	.....	.....
	1	12:02	24.6	21.6	0.82	27.8	1.27 (1.88)**	70.8 (69.6)**	62.7
	2	1:02	25.4	24.6	0.84	43.6	1.61 (1.88)	80.5 (79.9)	78.9
	3	2:02	27.1	24.2	0.82	50.6	1.75 (1.88)	78.2 (77.9)	82.6
	4	3:02	26.1	24.5	0.77	50.7	1.88 (1.88)	78.2 (78.7)	81.4
	5	4:02	.....	.....	.....	.....	2.02	.....	.....
Case 9 (G. T. B.).. 5/23/16 54.4 Kg. 1.56 Sq. M.	Prelim.	11:04	.....	.....	.....	.....	.....	.....	.....
	1	12:04	20.8	18.3	0.82	29.5	0.380	61.1	60.6
	2	1:04	20.3	17.9	0.82	28.5	0.380	59.8	62.2
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
G. T. B. ..... 5/25/16 55.5 Kg. 1.56 Sq. M.	Prelim.	9:55	.....	.....	.....	.....	.....	.....	.....
	1	10:25††	12.4	9.9	0.91	22.6	1.219	39.7	32.3
	2	11:25	27.2	22.8	0.87	42.1	1.219	75.7	76.9
	3	12:25	27.4	24.0	0.83	40.4	1.219	79.0	75.7
	4	1:25	26.7	23.8	0.82	37.4	1.219	78.0	79.3
	5	2:25	27.9	24.9	0.81	40.6	1.219	81.7	84.5

** Figures in brackets based on assumption that the maximum nitrogen excretion represents true protein metabolism for whole experiment.
‖ 62-minute period. ¶ Per hour. ‡ 57-minute period. †† 30-minute period.

—IN DWARFS AND LEGLESS MEN—(*Continued*)

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Lin.)	
.....	.....	....	.....	.....	..	..	..	....	47.7	Excluded from averages on account of restlessness
.....	36.7	60	.....	.....	..	..	..	....	....	Basal; in bed
49.9	36.6	58	7	0.82	..	..	..	....	....	Very quiet; asleep 30 minutes
56.5	36.7	60	7	0.77	..	..	..	....	....	Very quiet
.....	.....	....	.....	0.79	10	63	27	1.01	41.3	
.....	36.9	....	78	.....	..	..	..	....	....	8:30 to 9:50 a. m. ate 600 gm. beef containing 24.6 gm. N.
68.5	36.9	14	76	0.79	44	40	16	....	58.1	Fairly quiet
76.3	36.9	16	88	0.85	44	29	27	....	58.4	Fairly quiet
84.9	37.0	22	84	0.88	44	24	32	....	59.0	Fairly quiet; voided
79.7	37.0	13	83	0.85	46	28	26	....	56.4	Quiet
.....	36.5	....	.....	.....	..	..	..	....	....	Basal
52.5	36.5	68	1	0.83	..	..	..	....	....	Awake; motionless
49.7	36.4	64	1	0.81	..	..	..	....	....	Awake; motionless
.....	.....	....	.....	0.82	31	43	26	1.28	42.2	9:00 to 10:05 a. m. ate 662 gm. beef containing 23.2 gm. N.
.....	36.9	....	.....	.....	..	..	..	....	....	
71.7	37.1	77	4	0.85 (0.88)**	47 (72)**	28 (11)**	25 (17)**	1.72 (1.69)	57.1 (56.1)	Asleep 60 minutes. Motionless
78.8	37.2	83	12	0.86 (0.90)	53 (63)	19 (12)	28 (25)	1.96 (1.94)	65.0 (64.5)	Awake; very quiet
81.6	37.2	84	12	0.83 (0.84)	59 (64)	23 (20)	18 (16)	1.90 (1.89)	63.0 (62.8)	Awake; very quiet
78.1	37.1	79	10	0.72 (0.72)	64 (64)	34 (34)	2 (2)	1.90 (1.90)	63.0 (63.0)	Awake; very quiet
.....	36.8	....	.....	.....	..	..	..	....	....	Basal; normal control
63.9	36.9	58	6	0.83	..	..	..	....	....	Almost motionless
63.3	36.9	58	8	0.83	..	..	..	....	....	Almost motionless
.....	.....	....	.....	.....	17	47	36	1.11	38.7	8:30 to 9:15 a. m. ate 600 gm. beef containing 23.7 gm. N.
.....	36.9	....	.....	.....	..	..	..	....	....	
34.0	36.9	60	0	0.94	24	15	61	....	....	Motionless
75.4	37.0	66	12	0.92	43	17	40	....	....	Almost motionless
80.3	37.1	64	17	0.86	41	39	20	....	....	Almost motionless
77.5	37.1	64	17	0.82	42	35	23	....	....	Almost motionless
85.2	37.1	72	17	0.82	40	37	23	....	....	Almost motionless

more rapidly than the nitrogen, as first shown in dogs by Rubner[26] and in humans by Wolf.[27] Rubner's figures were taken in six-hour periods and show how long continued is the high nitrogen excretion after a meat diet containing 24.7 gm. nitrogen.

The sulphur elimination is shown in Table 2 to be very much more rapid. One would expect the nitrogen to sulphur ratio to be 16, which is that found in meat, but because of the variation in speed of excretion, the ratio falls during the first six hours and is too high in the following periods.

Our observations, which are made in very much shorter periods and extend only to seven hours after food, confirm these findings, except that in the hour during the ingestion of food the nitrogen excretion rises markedly; the sulphur increases but little. This is probably due to the rapid elimination of the extractives in the meat.

This delayed elimination of nitrogen after marked protein ingestion makes its hourly excretion a poor index of the metabolism during that hour. Since the total metabolism stays at a nearly constant level throughout the observation after food, it seems probable that the protein metabolism also stays at a constant level. The same value ought, therefore to be used throughout the observation, not a different one for each hour. The best value to use seems to be the maximum hourly nitrogen excretion and this has been used in all calculations. The effect of this choice is but slight in regard to the height of the total hourly metabolism, but the percentage of calories derived from the three foodstuffs is markedly affected, particularly in the early hours of the observation. This effect can be seen in Table 4, in which, in the case of R. De P., the calculations are made in both ways: (1), using the N as excreted; and (2), using the maximum value as the hourly excretion. The figures for Louis M. will be found in Paper 4 of this series.

The tables show quite clearly that no matter which value is assumed as the true protein metabolism, in the first hours of the observation a large part of the specific dynamic action is at the expense of the oxidation of carbohydrates. This is true of all cases except that of Louis M., in whom the 100 gm. of fat taken with the meat probably affected the relationship. This finding is not in accord with the results of Gigon.[28] He used casein and found that the specific dynamic action was due to protein metabolism alone, and that carbohydrate and fat were even spared slightly. Gigon's results on the increased heat production fol-

26. Rubner, Max: Die Gesetze des Energieverbrauchs bei der Ernährung, Leipzig, 1902, p. 369.

27. Wolf, C. G. L.: Die Ausscheidungszeit von Stickstoff, Schwefel und Kohlenstoff nach Aufnahme von Eiweisssubstanzen und Spaltungsprodukten, Biochem. Ztschr., 1912, **40,** 234; ibid., 1912, **41,** 111.

28. Gigon, A.: Ueber den Einfluss der Nahrungsaufnahme auf den Gaswechsel, Arch. f. Physiol., 1911, **140,** 509.

lowing casein ingestion are of interest in relation to the percentage increase which we have found. The results obtained by Gigon were recalculated by Williams, Riche and Lusk,[20] and the chart of their findings is here reproduced (Table 5). It shows an average specific dynamic action (70) which is lower than that reported in this paper (76). This difference is possibly due to the different form of protein ingested.

Staehelin[29] obtained, in one observation, results which are quite different from those of Gigon or from those here reported. He used a Jaquet apparatus, determining the metabolism in two hourly periods. The test meal consisted of 75 gm. of protein and 12.2 gm. of fat. In the twelve-hour observation following the meal the urine nitrogen increased 0.37 gm. per hour, which represents 9.9 calories of increased protein metabolism. The respiratory observation, however, indicates

TABLE 5.—INCREASE OF METABOLISM IN MAN DUE TO PROTEIN INGESTION (GIGON)

Food Casein, Gm.	Increase in Protein Metabolism		Increase in Total Calories of Metabolism	100 Calories of Protein Metabolism Increases Total Calories by
	Gm.	Calories		
50	7.1	28.4	19	67
100	23.8	95.2	53	56
150	35.7	142.8	118	83
200	58.1	232.4	171	74
Average				70

an average increased elimination by the body of 24.6 calories per hour and an increase in the proportion of fat metabolized. This result is not in accord with the other experiments here recorded.

Another conclusion may be drawn from the observations as viewed in Table 6. The relationship between the normal and abnormal cases shows that the specific dynamic action did not follow the surface area. The three normal cases have values per square meter which are very close together. The percentage increase of the two abnormal cases, however, is distinctly higher, which shows that diminishing the surface area or muscle volume did not proportionally reduce the intensity of the specific dynamic action. In the last column of the chart is shown the total percentage increase, found by dividing the actual increase in metabolism by the calories of extra protein oxidized. If one allows for the increased heat due to the fat ingestion of Louis M., the ratios

29. Staehelin, R.: Versuche ueber Gaswechsel und Energieverbrauch nach Nahrungsaufnahme, Ztschr. f. klin. Med., 1908, **66**, 201.

are all closely related. We interpret this to mean that the specific dynamic action is dependent in these cases on the total protein metabolism. It is certainly independent of the mass of muscle tissue.

NORMAL CONTROLS

In the course of these experiments and of those recorded in Paper 20 of this series there have been six basal observations on normal men between the ages of 23 and 34. Four are new subjects whose metabolism has not been previously determined.

The basal metabolism of E. F. D. B. was determined four times in the spring of 1913, when an average value of 39.8 calories per square meter per hour was found. In May, 1915, the metabolism by the same index was 37.6 calories. In May, 1916, the height of his metabolism was 38.4 calories. This shows the constancy of the basal metabolism of some normal individuals.

TABLE 6.—SPECIFIC DYNAMIC ACTION. PERCENTAGE INCREASE

Name	Physical Condition	Urinary Nitrogen		Calories Extra Protein Metabolished per Hr. Extra N × 28.5	Actual Calories Increase per Sq. M. per Hr.	100 Calories of Protein Metabolism Increases Cals. per Sq. M. by	Actual Total Calories Increase per Hr.	100 Calories of Protein Metabolism increases Total Calories by
		Basal, per Hr.	After Meat, per Hr.					
R. DeP.	Achondroplasia	0.60	1.86	33.9	19.4	57.2	24.1	71.1
Harry J.	Legless man	0.21	1.30	28.9	16.6	57.5	22.3	77.2
Louis M.*	Normal control	0.52	1.14	16.4	8.3	50.5	15.3	93.1*
W. B.	Normal control	0.38	1.22	22.3	11.7	52.6	18.2	81.8
S. K.	Normal control	0.46	1.29	22.0	11.1	50.5	16.6	75.5

* Regular protein meal plus 100 gm. of fat.

The metabolism of J. H. M. had been determined by the Benedict unit apparatus and reported in the series of Palmer, Means and Gamble,[30] and of Means.[2] The average of these observations is 39.4 calories per square meter per hour. These findings were made more than a year before our determination (39.5 calories) and on a different type of apparatus.

The average calories per square meter per hour of these six controls is 38.9. The average found in this laboratory for normal men between the ages of 20 and 50 is 39.7 calories per square meter per hour. The six controls reported here average 2 per cent. below this figure (Table 7).

30. Palmer, W. W., Means, J. H., and Gamble, J. L.: Basal Metabolism and Creatinin Elimination, Jour. Biol Chem., 1914, **19**, 239.

TABLE 7.—Summary of Basal Metabolism of Six Normal Controls. Men

Name	Date	Age	Height, Cm.	Weight	Surface Area, Sq. M. Linear Formula	Calories per Sq. M. per Hour	Variations from Average Normal 39.7 %	Average R. Q.	Total Calories Measured		Divergence of Direct from Indirect, per Cent.
									Indirect	Direct	
E. F. D B.	4/12/16	34	179.5	76.47	1.94	38.8	−2.2	0.80	150.71	161.79	+7.4
	4/25/16*	..	.....	.....	1.95	37.6	−5.4	0.80	73.23	71.54	−2.3
J. H. M.	4/21/16	30	177.0	75.34	1.89	39.5	−0.6	0.80	149.12	155.04	+4.0
J. C. F.	4/27/16	23	178.0	64.29	1.75	41.7	+5.1	0.82	146.05	149.18	+2.2
J. C. A.	4/29/16	26	175.3	60.20	1.64	39.2	−1.3	0.86	128.46	149.49	+16.3
S. K.	5/16/16	33	161.5	49.56	1.50	36 8	−7.4	0.79	110.31	114.84	+4.1
G. T. B.	5/23/16	25	164.5	54.37	1.56	38.7	−2.4	0.83	120.87	127.17	+5.2
Average	.....	..	.....	.....	....	38.7	−2.4	....	.....	.....	+5.7

* One hour experiment. All others two hours.

SUMMARY

1. The basal metabolism of five dwarfs, two legless men and six normal controls is reported. The legless men and the dwarfs, with apparently normal endocrine systems, showed, in relation to their surface area, the same level of metabolism as normal men. The law of surface area holds good for men of unusual body shape.

2. The dwarfs with involvement of the ductless glands and symptoms of cretinism showed a marked reduction in metabolism below the average found in normal cases, as has been reported by other authorities.

3. Following the ingestion of large quantities of meat, the excretion of urinary nitrogen during the earlier hours is not an accurate index of the protein metabolism. The sulphur excretion is more rapid than the nitrogen excretion.

4. The stimulation of metabolism following a large amount of meat is almost at its height two hours after the meal is eaten. The extra heat produced may amount to three-quarters of the calories in the protein metabolized, and may lead to an increase of 46 per cent. above the level of the basal heat production.

5. The specific dynamic action of a meal containing 24 gm. of nitrogen in the form of meat was larger in the case of a legless man, and of an achondroplastic dwarf, with very small arms and legs and normal trunk, than in the cases of three normal controls of greater weight and greater surface area. This indicates that the intensity of the specific dynamic action is not proportional to the mass of the musculature. The true explanation of the results cannot be given in the light of present knowledge. Various possible explanations come naturally to mind, such, for example, as a greater concentration of amino-acids in the blood flowing to the muscles, or the presence of a liver, which, in proportion to the size of the organism, is relatively larger than the normal.

477 First Avenue.

CLINICAL CALORIMETRY

TWENTY-SECOND PAPER

THE RESPIRATORY METABOLISM IN NEPHRITIS*

JOSEPH C. AUB, M.D., AND EUGENE F. DU BOIS, M.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM
NEW YORK

A study of the syndrome known as *nephritis* should throw a great deal of light on many problems of normal and pathologic physiology. The disease is accompanied by profound changes of long duration, and the organism is obliged to adapt itself to conditions which are very different from those found in health. For this reason the investigator can obtain in the study of nephritis much information as to the manner in which the total metabolism is influenced by certain factors. Chief among these are nitrogen retention, edema, high blood pressure, acidosis and the conditions which cause uremia. Unfortunately, we know little about these factors, and suspect the presence of many more about which we know nothing. At this stage, all that one can do is to present his findings as completely as possible in the hope that they will be of service to those who can some day solve the nephritis problem. In the meantime, the study will help in the solution of many related questions.

The basal metabolism of patients with cardiac and renal disease was discussed briefly in Paper 16 of this series. The literature was reviewed and the results obtained on sixteen patients were published in such detail as was possible. Some of these patients had been studied in the early days of the calorimeter, before the general recognition of the importance of many of the modern measurements and tests. In most of the patients studied the cardiac element predominated, but in about half there was an important nephritic element also. It was found that the total metabolism of patients with mild cardiac or renal disease was normal, and that five of the twelve patients with dyspnea showed an increase in metabolism of 25 to 50 per cent. The respiratory quotients were all within normal limits and the method of direct calorimetry gave results only 1.9 per cent. lower than the method of indirect calorimetry. No direct relationship was found between the level of the metabolism and the acidosis, height of blood pressure or the ability of the kidney to excrete phenolsulphonephthalein. In

* Submitted for publication Dec. 19, 1916.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

Table 2 of Paper 16 the results of the clinical and laboratory findings were compared.

This present work is a continuation of Paper 16 and Tables 2 and 3 have been made to correspond as closely as possible with Table 2 of the previous publication. More attention has been given to blood analyses, the methods for estimating the degree of acidosis, and the functional capacity of the kidneys. The patients were all primarily nephritics and were selected from a large number in the effort to obtain young people with few complications. For the first time since the calorimeter work was begun, patients with an absolutely bad prognosis were used as subjects.

METHODS

The men patients were studied in the metabolism ward and calorimeter fully described in previous papers. The two women patients could not be brought to the metabolism ward, and it was impossible to study their intake and output, but otherwise they were treated in just the same manner as the men. Patients with orthopnea were placed in the steamer chair while in the calorimeter; all others used the bed, with head rest and pillow. Most of the patients were given a cup of "caffein-free" coffee (Kaffee Hag) without cream or sugar, early in the morning of the experiment. Except for this they were all fasting, having received no food since the previous afternoon. While in the apparatus they were all quiet, except the uremic patients, Isadore R. and Frank C.

The blood pressure was measured by the Faught apparatus, diastolic readings being made at the diminution of the murmur in the artery, which usually occurs just before its disappearance. The phenolsulphonephthalein test of Rowntree and Geraghty was used, the results in the tables being expressed as the total excretion in two hours and ten minutes. The carbon dioxid combining capacity of the plasma was determined by the Van Slyke method.

The blood and urinalyses, while the patients were in the metabolism ward, were made by Dr. Frank C. Gephart of the staff of the Russell Sage Institute of Pathology. While the patients were in the general medical wards the analyses were made, for the most part, in the Pathological Department of Bellevue Hospital by Drs. A. O. Gettler and Willis Baker. To them and to Dr. Norris we are indebted for permission to publish the results. These authors have recently published a valuable contribution on the "Chemical and Physical Analysis of Blood in Thirty Normal Cases."[1]

DISCUSSION OF RESULTS

The manifestations of nephritis are so varied that it will require the study of many cases to give all the information that is needed. Nevertheless, much can be learned from the ten cases summarized in Table 2 and the sixteen cases of the previous publication. (See Table 2, Paper 16).

Direct and Indirect Calorimetry.—In the thirteen[2] experiments here reported the total calories, as measured by the method of indirect

1. Gettler, A. O., and Baker, Willis: Jour. Biol. Chem., 1916, **25**, 211.
2. The experiment on Mildred C. is omitted because the direct method could not be used.

calorimetry, was 1,700.4; by the method of direct calorimetry, 1,743.3, or 2.5 per cent. higher. In the previous work, the calories by the indirect method totaled 4,297.7, and by the direct method, 4,214.5, which was 1.9 per cent. lower. These two divergences of the direct calorimetry almost neutralize each other, and in the grand total of all the work the indirect is 5,998.1; the direct, 5,957.8, which is 0.7 per cent. lower. This agreement is just as close as in the case of a group of normal controls, and it shows that the calorific value of one liter of oxygen is the same in nephritics and normals. We must not forget, however, that there may be striking changes in the intermediary metabolism without great change in the calorific value of oxygen. This is brought out clearly in the work on diabetes.

Respiratory Quotients.—Except in the cases of diabetes and in convalescence, the respiratory quotient fourteen hours after the last meal is little more than the expression of the amount of carbohydrate available in the organism. This depends on the state of nourishment, the amount of carbohydrate food taken the preceding day, and the level of the total metabolism which determines the rate at which this carbohydrate is oxidized. Nephritic patients, as a rule, are given carbohydrate diets unless the total calories are greatly restricted. It is not surprising, therefore, that quotients as high as 0.93 and 0.89 were found. On the other hand, the lowest quotients obtained, 0.77 and 0.78, are well within normal limits. This confirms the statement made a year ago that there is no need to assume any change in the type of the metabolism from the normal.

Total Metabolism.—The calculations of the total metabolism are based on the measurements obtained by the method of indirect calorimetry and are expressed as calories per square meter of surface per hour. This figure is then compared with the standard average normal figure for the same age and sex, as given in Table 7 of Paper 13 of this series, and the percentage variation from the normal recorded. Most of the subjects could be compared with the group of normal men between the ages of 20 and 50, the average calories per square meter per hour being 39.7. The results obtained on John C., 62 years old, were compared with the figure 37, which is about the average for his time of life according to the revised curve given in Paper 19. This makes him 10 per cent. above the normal. He still had his youthful vigor, and it is well to remember that his metabolism was only 3 per cent. above the standard for men 20 to 50 years of age. Edna S. presents a different problem. She was only 13 years old, and the standard for girls of this age is 47 calories per square meter per hour. For two months before the calorimeter observation she had been on a restricted

diet, and this may reduce the metabolism even more in a child than in an adult. Direct evidence on this point is lacking, but it can be seen in Table 9 of Paper 17 that the four children with severe diabetes show an unusual reduction in metabolism. The observation on Frank C., with uremia, was almost spoiled by his restlessness, which was even greater than is indicated by the high work-adder. The results were 29 per cent. above the basal standard, but those who observed him were confident that his muscular activity alone could have increased his metabolism 20 to 30 per cent., and it is doubtful if his basal metabolism would have been higher than the average normal. It is unfortunate that the otherwise satisfactory experiment on Mildred C. should be marred by the possibility that she had exophthalmic goiter. Her nervous temperament and exophthalmos, which was greater than is generally found in nephritis, suggested this factor.

A. Influence of Dyspnea.—Isidore R., Frank C., and John C. were distinctly dyspneic, and they all showed a slight increase in metabolism. This increase was not as marked as in the four out of five patients with moderately severe dyspnea described in the paper on cardiacs and nephritics.

B. Acidosis.—According to the carbon dioxid combining capacity of the plasma, a rather severe type of acidosis was present in the case of Joseph U. on April 5, and in Isidore R. on January 24. The former showed a metabolism of 7 per cent. below the normal; the latter, only 2 per cent. above. Slight acidosis was found in Joseph U. on April 10, and in Jack K. on March 4. Their figures were —12 per cent. and +5 per cent., respectively. These results, taken with the figures obtained in Papers 16 and 17, indicate that acidosis has little effect on the total metabolism.

C. Edema.—There was marked edema in the cases of Joseph U., Lee H., Edna S. and William S. The first three showed a distinct reduction in metabolism. With Adam P., January 14, the edema was moderate and the metabolism 10 per cent. below the average normal. In general, the type of nephritis with edema is accompanied by a reduction in metabolism; the type without edema, by a slight increase in metabolism. One naturally expects an organism diluted by inert fluid to show a diminished metabolism according to body weight. Obesity patients have such a reduction, but Means has proved that they have the same metabolism per square meter of surface as normal people.[3]

3. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour. Med. Research, 1915, **32**, 121; The Basal Metabolism in Obesity, THE ARCHIVES INT. MED., 1916, **17**, 704.

Edematous cardiac patients as a rule show an increased metabolism, but here other factors may be involved. The reduction of metabolism per square meter of surface found in nephritic edema is sometimes very marked (—27 and —40 per cent.), and it points to some cause other than mere dilution of tissue and distention of skin.

D. High Blood Pressure.—All the patients except Lee H. showed a rise in blood pressure. The systolic pressure was above 200 mm. in the cases of Adam P., January 14, Isidore R., Frank C., John C. and Mildred C. Of these, Adam P. showed a reduced metabolism and the others an increase. With Adam P. the metabolism was about the same when his systolic pressure was 185 mm. as when it was 230 mm. George M., of Paper 16, showed exactly the same figures for a blood pressure of 160 mm. as for a pressure of 195 mm. On the other hand, Joseph U. showed a drop in metabolism when his blood pressure fell. Blood pressure has no constant influence on the total metabolism.

E. Eliminative Power of the Kidney.—Curiously enough, most of the patients were able to eliminate at least 6 gm. of nitrogen in the urine on the calorimeter days, and Lee H. was the only one, except the incontinent patients, Isadore R. and Frank C., in whom the urine volume was much diminished. On the other hand, the chlorid elimination was low in most of the patients, probably on account of the low intake in some cases, but in most on account of inability on the part of the kidney to excrete salt. The phthalein output was low in all cases except Joseph U. on April 5, and Lee H. on December 4. The Ambard coefficient expressed in terms of the McLean index was low in the cases of Joseph U. and Frank C.

The nonprotein nitrogen was above the normal limits in the cases of Joseph U., Jack K., Isidore R., Frank C.; and the urea nitrogen was above normal in Lee H. also. One of these patients showed a decrease in metabolism, the others a slight increase. In general, it does not seem that the products retained by damaged kidneys have any direct effect on the level of the total metabolism.

CHANGES IN INDIVIDUAL CASES

Joseph U. was in the calorimeter three times, and during the whole period there was little change in the McLean index and blood urea. In the first experiment his metabolism was higher than normal. In the next week he lost 5 kg. of edema and his metabolism fell to 7 per cent. below the normal average. At this time he had a distinct acidosis and furnished an excellent opportunity to study the effect of this factor on metabolism. Accordingly, he was given sodium bicarbonate until the acidosis almost disappeared and there was scarcely any change in his metabolism.

Lee H. was studied, December 4, and again a month later, when he had gained 5.5 kg. of edema. During this same period there was a marked fall in the phthalein output and increase in the retention of urea and creatinin. His metabolism in the first test had been 12 per cent. below the average normal; a month later it was 27 per cent. below. Part of this decrease was undoubtedly due to rest and low diet.

Adam P. was in the calorimeter January 14 and again three and a half weeks later, when he had lost 8 kg. of edema. In this interval there was practically no change in the phthalein excretion or in the blood urea, but the blood pressure fell 45 mm. There was hardly any alteration in the level of his total metabolism.

SUMMARY AND CONCLUSIONS

Ten patients with nephritis were studied in the calorimeter. All were severe cases, and it was possible to examine five of the patients shortly before death. The results have been compared with those obtained last year on a series of patients with cardiorenal disease, six of whom were primarily nephritics.

In the present series nine experiments were made on edematous subjects. All but two of these tests showed a diminution of the basal metabolism, both according to body weight and to surface area. In two cases with great edema the heat production was 27 and 40 per cent. below the normal average.

Five patients suffering from nephritis of the chronic interstitial type, without edema, were studied. One with marked uremia was at the normal level of metabolism. Another, who was very restless, showed an increase. A third, in whom hyperthyroidism was suspected, also showed an increase. The other two were near the upper normal level of metabolism.

In most of the patients with greatly increased blood pressure the metabolism was higher than in the other nephritics with lower blood pressures. Most of the patients with marked dyspnea showed some increase in metabolism. No relationship could be established between the level of metabolism and the degree of acidosis or the eliminative power of the kidney, as estimated by the McLean index, the phenolsulphonephthalein test, the elimination of salt and nitrogen, and the analysis of the various substances in the blood, such as chlorids, urea, and the nonprotein nitrogen.

The methods of direct and indirect calorimetry in this and the previous series of cardionephritics give totals which agree within 0.7 per cent. The respiratory quotients are all within normal limits, showing that nephritics derive their energy from very much the same proportions of the various foodstuffs as do normal men.

The normal quotients found in patients with low carbon dioxid com-

bining capacity of the plasma prove that nephritic acidosis is not caused by difficulty in oxidizing carbohydrates.

Edematous nephritics kept on low diets show a reduction in food requirement similar to that usually found in prolonged undernutrition. Other nephritics have approximately the normal food requirement.[4]

CASE HISTORIES

CASE 1.—Joseph U., aged 19; chronic parenchymatous nephritis with acute exacerbation. Admitted March 27, 1916; died April 23, 1916.

History.—Five years prior to the test he had scarlet fever. Recently he has been a sign painter's helper but has not been much exposed to the danger of lead poisoning. His habits are good. For several years he has passed his water once or twice during the night. Early in March, 1916, after a wetting, he noticed edema of the eyelids, then edema of the ankles, disappearing at night. About March 20 the edema of the legs became permanent and a few days before admission the genitalia became edematous. He feels perfectly well.

Physical Examination.—Height 175 cm.; well nourished; color pasty; marked edema of face, back, genitalia, thighs and legs. Heart: Apex beat in the fifth space 11.5 cm. to the left of the median line. Left limit of dulness 12.5 cm. to the left; right limit, 3 cm. to the right of median line. Sounds are of good quality; no murmurs. Lungs are clear. There is marked acne of face and back.

The clinical data are given in Table 4 and a summary of the more important findings in Tables 2 and 3. His urine contained a large amount of albumin, pus casts and many granular casts; no glucose. The McLean indexes were as follows: March 31, 49; April 4, 46; April 10, 39. The CO_2 combining power of the plasma was as follows: April 4, 39 volume per cent.; April 5, 39 per cent.; April 8, 40 to 50 per cent.; April 9, 60 per cent.; April 10, 55 per cent.; April 16, 39 per cent.; April 19, 48 per cent.

Calorimeter observations were made on March 29, April 5 and April 10.

From March 29 to April 10 he was on a mixed diet containing about 1,500 calories, 5 gm. nitrogen and 1.5 gm. salt, with about 1,500 c.c. fluids in addition to the water of the so-called solid foods. He was given hot air baths almost every day, responding unusually well, losing between 480 and 900 gm. weight during the baths. His temperature was normal, he felt well and he lost 5 kg. weight in twelve days, the edema almost disappearing. During this period he passed 1,000 to 1,500 c.c. urine a day, containing from 10 to 13 gm. of nitrogen and 2 to 5 gm. of chlorids. The prognosis would have been favorable were it not for the low phthalein output on two occasions, the low McLean index, the high nonprotein nitrogen and high urea of the blood and the low carbon dioxid combining power of the plasma. The high phthalein output of April 4 stood in contrast to the other tests.

In order to eliminate the factor of acidosis he was given 40 gm. sodium bicarbonate between 6 p. m., April 8 and 6 p. m., April 9, the two days before the last calorimeter test.

On April 11 the picture changed markedly. He became very weak in the hot air bath and was removed at once. The temperature rose to 105 F. and remained elevated for five days. During this period his pulse was 98 to 124; respiration, 24 to 40. The edema increased. On the day after the onset,

4. The above work is a continuation of studies in cardiac and renal disease carried on a year previously in association with Dr. Francis W. Peabody of Boston. It is a pleasure to record the active participation of Dr. Peabody in about half of the experiments of this present series.

TABLE 1.—NEPHRITIS. DATA OF—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Case 1 (Joseph U.) 3/29/16 75.7 Kg. 1.84 Sq. M.	Prelim.	11:48	.....	.....	.....	.....	.....	.....	.....
	1	12:48	26.6	25.2	0.77	34.6	0.555	82.9	88.0
	2	1:58	26.8	25.1	0.78	35.5	0.555	82.9	86.9
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Joseph U. ..... 4/5/16 70.8 Kg. 1.83 Sq. M.	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
	1	11:58	22.6	22.6	0.73	28.8	0.375	73.9	77.2
	2	12:58	23.3	19.5	0.87	28.5	0.375	65.9	77.5
	3	1:58	22.7	18.3	0.90	28.5	0.375	62.5	78.0
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Joseph U. ..... 4/10/16 70.6 Kg. 1.83 Sq. M.	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
	1	12:27	28.6	21.2	0.81	22.5	0.408	70.7	74.2
	2	1:27	22.0	20.7	0.77	21.6	0.408	68.4	70.6
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 2 (Lee H.).... 12/4/15 55.1 Kg. 1.57 Sq. M.	Prelim.	11:00	.....	.....	.....	.....	.....	.....	.....
	1	11:57½	17.4	15.1	0.84	21.9	0.249	50.7	54.6
	2	1:00	19.7	17.1	0.84	26.0	0.249	57.7	61.7
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Lee H. ..... 1/5/16 61.6 Kg. 1.70 Sq. M.	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
	1	12:40	16.0	13.7	0.85	20.2	0.296	46.1	51.1
	2	1:41	17.5	16.1	0.79	22.5	0.296	53.4	57.2
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 3 (Edna S.)... 12/1/15 48.2 Kg. 1.39 Sq. M.	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
	1	12:39	14.2	11.0	0.94	18.0	0.713	38.1	40.0
	2	1:39	14.6	11.9	0.89	17.7	0.713	40.7	40.9
	3	2:09	7.2	5.4	0.96	8.6	0.713	18.9	20.7
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 4 (Adam P.) 1/14/16 60.5 Kg. 1.60 Sq. M.	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
	1	12:25	19.1	17.0	0.82	22.1	0.340	56.6	61.2
	2	1:25	19.0	17.6	0.79	21.6	0.340	58.3	62.8
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Adam P. ..... 2/7/16 52.5 Kg. 1.52 Sq. M.	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
	1	12:30	17.5	16.4	0.78	21.9	0.163	54.5	55.7
	2	1:30	17.1	14.8	0.84	21.3	0.163	50.0	54.1
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 10..... (Isidore R.) 1/24/16 62.2 Kg. 1.67 Sq. M.	Prelim.	11:58	.....	.....	.....	.....	.....	.....	.....
	1	12:28	13.0	11.9	0.79	17.9	.....	39.6	42.3
	2	12:58	13.8	12.6	0.73	19.5	.....	45.2	45.0
	3	1:28	11.3	9.5	0.90	15.6	.....	32.7	34.1
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....

Direct Calorimetry, Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Lin.)	
.....	37.1	....	.....	.....	..	..	..	....	....	Basal; in bed
84.4	37.1	66	19.0	0.76	..	..	..	....	....	Quiet; reading 15 minutes
81.2	37.0	66	19.0	0.77	..	..	..	....	....	Quiet; not reading
.....	.....	....	.....	.....	18	66	16	1.10	45.1	
.....	36.9	....	.....	.....	..	..	..	....	....	Basal; in bed
66.2	36.7	55	16.0	0.72	..	..	..	....	....	Quiet
79.6	36.7	55	5.0	0.88	..	..	..	....	....	Very quiet
73.6	36.7	55	15.5	0.92	..	..	..	....	....	Very quiet
.....	.....	....	.....	.....	15	66	19	0.95	36.9	
.....	36.9	....	.....	.....	..	..	..	....	....	Basal; in bed
74.0	36.9	62	12.0	0.81	..	..	..	....	....	Quiet; asleep 15 minutes
85.0	37.2	64	4.0	0.77	..	..	..	....	....	Motionless
.....	.....	....	.....	.....	16	61	22	0.99	38.0	
.....	36.6	48			..	..	..	....	....	Basal; in chair
48.4	36.5	44	15.0	0.84	..	..	..	....	....	Fairly quiet; dozed
54.1	36.4	44	15.0	0.84	..	..	..	....	....	Fairly quiet
.....	.....	....	.....	.....	12	44	44	0.98	34.5	{1st period–57½ min. {2d period–62½ min.
.....	36.8	61	.....	.....	..	..	..	....	....	Basal; in bed
54.9	36.9	67	10.0	0.86	17	41	42	....	....	Very quiet
52.4	36.8	68	14.0	0.79	15	62	23	....	....	{Very quiet, until end of period; 61 minute period
.....	.....	....	.....	...	..	..	..	0.80	29.0	
.....	37.0	....	.....	.....	..	..	..	....	....	Basal; in chair
37.3	37.0	62	1.0	0.94	..	..	..	....	....	Very quiet; reading
40.7	37.0	62	2.4	0.90	..	..	..	....	....	Very quiet
21.6	37.0	60	1.5	0.97	..	..	..	....	....	Very quiet; reading; 30 minute period
.....	.....	....	.....	.....	5	21	74	0.81	28	
.....	37.2									
55.9	37.1	58	6.0	0.82	16	52	32	....	....	Very quiet
58.0	37.0	59	25.0	0.78	16	63	21	....	....	Somewhat restless
.....	.....	....	.....	.....	..	..	..	0.95	35.9	
.....	36.9	....	.....	.....	..	..	..	....	....	Basal; in bed
53.3	36.9	60	13.0	0.77	8	71	21	....	....	Very quiet
49.6	36.8	58	15.0	0.84	9	50	41	....	....	Quiet
.....	.....	....	.....	.....	..	..	..	1.00	34.4	
.....	37.1	....	.....	.....	..	..	..	....	....	"Basal"; in bed; irrational
41.0	37.0	92	23.0	.....	..	..	..	....	....	Fairly restless; 30 min. period
44.8	37.0	96	30.0	.....	..	..	..	....	....	Restless; 30 min. period
38.2	37.1	....	0.0	.....	..	..	..	....	....	Asleep; very quiet; 30 min. period
.....	.....	....	.....	.....	..	..	..	1.24	41.9*	

* Results closer to true basal figures are obtained by using average R. Q. and taking CO_2 figures for first and third periods. This gives an average of 40.4 calories per square meter per hour.

TABLE 1.—NEPHRITIS. DATA OF—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Case 5 (Jack K.)... 3/4/16	Prelim.	11:58	.....	.....	.....	.....	.....	.....	.....
58.3 Kg. 1.62 Sq. M.	1	12:58	24.7	20.1	0.89	23.3	0.525	66.2	69.0
	2	1:58	23.9	19.6	0.89	25.1	0.525	66.3	75.1
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 6 (Frank C.) 2/28/16	Prelim.	11:46	.....	.....	.....	.....	.....	.....	.....
Missing 1.54 Sq. M.	1	12:44	23.2	23.4	0.72	21.1	0.525	.....	67.4
	2	1:21	18.1	14.2	0.92	16.0	0.525	.....	47.8
	Total 95 min.	.....	.....	.....	.....	.....	.....	124.8	
	Aver. per hr.	.....	.....	.....	.....	.....	.....	78.9	.....
Case 7 (John C.).. 2/9/16	Prelim.	.....	.....	.....	.....	.....	.....	.....	.....
69.8 Kg. 1.87 Sq. M.	1	12:40	24.3	23.9	0.74	22.3	0.276	78.4	81.7
	2	1:40	25.0	22.1	0.82	20.9	0.276	74.3	79.9
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Case 8..... (Mildred C.) 12/10/16	Prelim.	11:57	.....	.....	.....	.....	.....	.....	.....
49.7 Kg. 1.40 Sq. M.	1	12:57	19.9	16.6	0.87	21.6	0.231	.....	49.7
	2	1:57	21.4	23.1	0.68	31.6	0.231	.....	61.9
	Aver.	.....	.....	.....	.....	.....	.....	65.8	.....
Case 9 (Wm. S.)... 12/6/16	Prelim.	11:40	.....	.....	.....	.....	.....	.....	.....
64.2 Kg. 1.66 Sq. M.	1	12:40	22.2	20.9	0.77	26.1	0.483	66.8	66.3
	2	1:40	22.4	20.6	0.79	27.5	0.483	66.3	70.5
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....

bronchial voice and breathing were heard over the right lower lobe. Two days later there was a small area of dulness and bronchial breathing at the angle of the left scapula. April 16 the temperature was normal and the patient felt weak but much better. By the 19th he was drowsy and his respirations slow and deep. There was persistent flatness and diminished breathing over the right lower lobe, but only 2 c.c. cloudy, sterile fluid could be withdrawn by needle. On the afternoon of the 22d he suddenly began to have violent convulsions, lasting until his death, shortly after midnight. No necropsy could be obtained.

After the febrile attack, which was probably pneumonia, the urine volume diminished rapidly, with a marked fall in the output of nitrogen and salt. This was in part due to a diarrhea.

CASE 2.—Lee H., aged 21, Chinaman, cook; chronic parenchymatous nephritis with acute exacerbation. Admitted Nov. 19, 1915, died Jan. 14, 1916.

History.—It was impossible to get any information as to the character of his previous illnesses. He says that he has always been well. He has been in New York five years. He says his present trouble began about Nov. 1, 1915.

Physical Examination.—Height 170 cm.; frame small, whole body, including face and scalp, markedly edematous. His color is pasty; he is orthopneic and dyspneic. Heart: Apex beat in the fifth space 10 cm. from median line; no murmurs. Lungs: At both bases, flatness, diminished breath sounds and

—CALORIMETER EXPERIMENTS—(*Continued*)

Direct Calorimetry, Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Lin.)	
.....	36.9	72			..	..	..	....	....	Very quiet; basal Asleep 35 min.
63.4	36.8	60	5.0	0.92	..	..	..	....	....	Reading 10 min.
68.0	36.7	68	13.5	0.92	..	..	..	....	....	Very quiet; awake
.....	.....	....	.....	.....	21	23	56	1.2	41.5	
.....	37.0	88	.....	.....	..	..	..	....	....	Basal (restless)
71.0	37.1	86	47.0	.....	..	..	..	....	....	58 min. period; very restless
50.6	37.2	89	54.0	.....	..	..	..	....	....	37 min. period; very restless
76.8	.....	....	.....	0.80	18	57	25	1.6	51.2	Very unsatisfactory observation
.....	37.2	63								
74.9	37.1	57	19.0	0.74	..	..	..	....	....	Very quiet
75.5	37.1	60	18.5	0.83	..	..	..	....	....	Quiet
.....	.....	....	.....	0.78	10	68	22	1.1	40.8	
.....	.....	104	.....	.....	..	..	..	....	....	Basal; in chair
.....	.....	103	5.0	0.88	..	..	..	....	....	Very quiet; slept
.....	.....	104	11.0	0.66						
.....	.....	....	.....	0.77	9	73	18	1.32	47.0	Rectal thermometer out of order
.....	38.1	85								
74.9	38.3	86	6.0	0.76	..	..	..	....	....	Quiet
71.1	38.3	83	5.0	0.79	..	..	..	....	....	Quiet
.....	.....	....	.....	.....	19	62	19	1.07	41.2	

fremitus. Radial arteries slightly thickened. Eyegrounds normal. Abdomen contains some fluid.

Patient was in the calorimeter December 4 and January 5. For clinical data December 4 and January 5 to 12, see Table 6, and also the summary, Tables 2 and 3.

The urine contained a large amount of albumin and many hyaline and granular casts. The specific gravity was high, usually in the neighborhood of 1.040. Glucose was absent. On some examinations red blood cells were found in the urine. The Wassermann test was faintly positive on three examinations. November 24 the blood urea was 32 mg.; creatinin, 0.84 mg.; chlorids, 0.51 mg.; freezing point, —0.647 C.; December 4, alveolar CO_2 38 mm. Hg; January 4, blood urea was 49 mg.; ammonia nitrogen, 1.1 mg.; chlorids, 0.612 per cent.; creatinin, 3.9 mg.; CO_2 combining capacity, 70 per cent. The phenolsulphonephthalein excretion in two hours was as follows: December 3, 64 per cent.; December 18, 44 per cent.; January 12, 13 per cent.

The blood pressure was not increased: Systolic, 115 to 120 mm.; diastolic, 75 to 85 mm.

The patient was kept on a moderately restricted diet and was given hot packs. His edema continued to increase but the dyspnea and orthopnea were not distressing and the patient remained cheerful. The physical signs of fluid in the pleural cavities and abdomen were practically unchanged.

January 4 he began to have fever in the afternoons, reaching 101 to 103 F., with morning remissions. He complained of pain in the abdomen and chest and began to cough. Over the lungs, anteriorly, there developed many moist, crackling râles, and over the precordium a cardiorespiratory friction rub. The urine volume fell to 600 to 900 c.c., with 11 to 17 gm. nitrogen and only a trace of chlorids. His bowels moved four to seven times a day. The patient grew more toxic and dyspneic but had no convulsions. He died, January 13. Postmortem aspiration of the pleural cavities and abdomen yielded milky fluid containing very few cells, but many diplococci. There was no necropsy.

The blood on January 7 showed hemoglobin, 75 per cent.; red blood cells, 4,500,000; leukocytes, 10,000; no filaria.

CASE 3.—Edna S., aged 13, schoolgirl, born in New York. Admitted Oct. 7, 1915; died May 2, 1916; chronic parenchymatous nephritis with acute exacerbation.

History.—Previous history negative except for measles and a mild sore throat. In 1912 she had a cough for a month and went to a physician who said she had kidney trouble. For the previous two years she had had frequent nosebleeds, but no frequency of micturition, headache, dizziness or edema until the present trouble. Sept. 1, 1915, her mother noticed edema of the face. October 4 she was put to bed by the family physician on account of edema of the legs. October 6 she lost her vision and had a convulsion of the right side of the body, and was also in a convulsion when she was brought to the hospital the next day.

Physical Examination.—Color pasty; face, body and extremities very edematous. The patient is a well nourished, intelligent girl, orthopneic and slightly dyspneic. Respirations, Cheyne-Stokes. Tonsils large, with deep crypts. Heart: Left border of dulness in the fifth space 2 cm. to the left of the midclavicular line; right border 2 cm. to the right of the midsternal line. The second sound in the aortic area is markedly accentuated; no murmurs. The liver edge is felt 2 cm. below the free margin of the ribs. The fundi of the eyes show slight haziness of the disk outlines. The blood pressure, which was 160 mm., dropped to 115 mm. after removal of 350 c.c. blood from vein.

On repeated examinations the urine showed large amounts of albumin, many hyaline and granular casts, and sometimes red blood cells. It was acid, contained no glucose, and the specific gravity averaged about 1.020.

The patient was given a restricted diet, with fruit and plenty of carbohydrate, but very little nitrogen and only small amounts of fluid. She was also given a daily hot pack. November 15 and again March 3 she had convulsions during which venesections were performed. In November and December there was little change in her general condition, the edema being extreme and the urine volume always scanty. The patient was in the calorimeter December 1.

January 28 fluid began to collect in the left pleural cavity. April 18 the temperature, which had been normal, rose to 101 F., then became very irregular, reaching 106 F., April 29. Cough and pain in the chest developed. She became more and more toxic and stuporous and died May 2, 1916. No necropsy could be obtained.

The phthalein tests were as follows: November 15, 16 per cent.; November 23, 61 per cent.

The blood tests: November 15: urea nitrogen, 14.5 mg.; November 18: urea nitrogen, 22.6 mg.; November 30: nonprotein nitrogen, 18.9 mg.; March 3: total nonprotein nitrogen, 19.7 mg.; urea nitrogen, 16.2 mg.; blood CO_2 combining power, 62 volume per cent.

The spinal fluid, March 3, removed when the patient was stuporous, ten minutes before the convulsions began, was under increased pressure.

CASE 4.—Adam P., aged 26, Russian, a tailor. Admitted Jan. 10, 1915; discharged improved, May 5, 1916; chronic parenchymatous nephritis with acute exacerbation.

History.—His father was a heavy drinker. At the age of 15 the patient had rheumatic fever for two months, involving many joints. Since then he has had some subacute symptoms. Six months prior to the test he had tonsillitis. He uses beer in moderation.

About April, 1915, he noticed edema of the legs, which has gradually increased and has involved abdomen, arms and face. Shortly afterward, he began to suffer from dimness of vision, dizziness and headaches. He has had increasing nocturia and now passes urine three to four times at night.

Physical Examination.—A well developed young man with marked generalized edema. He is not dyspneic. Heart: Left border of dulness 12.5 cm. from the median line. The second pulmonic sound is accentuated. At the bases of the lungs there is some dulness and diminution of breath sounds. Eyes: Fundi show chorioretinitis of long duration. He can distinguish fingers only at a distance of 2 feet. Dr. Rees believes that the eye condition has nothing to do with the nephritis.

The urine contained a large amount of albumin and many hyaline and granular casts. The specific gravity varied between 1.016 and 1.025. On admission the blood analysis was as follows:

Sugar	90 mg.
Urea nitrogen	34.3 mg.
Ammonia nitrogen	0.25 mg.
Creatinin	0.5 mg.
Uric acid	3.7 mg.
Plasma chlorids	0.60 per cent.

The phthalein test in two hours was 27 per cent. and the McLean index was 67.

The blood pressure was about 200 mm. systolic and 130 mm. diastolic until February 3; then it fell to about 160-105 mm.

The patient was given a restricted diet and, at first, hot packs. The generalized edema and hydrothorax continued. He was in the calorimeter January 14. At this time there were about 10 kg. of retained fluid in the edema. The daily urine volume was 1,000 to 1,500 c.c.; urine nitrogen, 8 to 11 gm.; chlorids, 5 to 8 gm. The patient lost weight steadily and when next in the calorimeter, February 7, had almost no edema. The McLean index February 8, was 25. The output of water, nitrogen and chlorids in the urine exceeded the intake. The calories in the diet were just about sufficient to cover the requirement. The volume per cent. of CO_2 in the plasma was as follows: January 13, 58; January 18, 62; February 8, 66.

The patient continued to improve slowly and by March 5 had no edema and no dyspnea and was able to get out of bed for a few hours. He was still unable to distinguish fingers at a greater distance than 4 feet. March 5, after walking a few steps, he complained of pain in the back. The next day the urine contained blood. For the following week he had pain over the right kidney, slight fever, many pus cells and a few red blood cells in the urine. The Roentgen ray revealed no calculus. Infarction of the kidney was suspected.

The pus in the urine disappeared in a few weeks. On March 17 the urine culture showed streptococci. He grew stronger and on May 5 was sent to a convalescent home. While on measured diets several experiments were made to determine the effect of sodium bicarbonate on his weight and the carbon dioxid combining capacity of his plasma.

Case 9.—William S., aged 27, laborer, was admitted to the Fourth Medical Division, service of Dr. Nammack, Nov. 16, 1915; discharged improved Feb. 4, 1916; chronic parenchymatous nephritis.

History.—At the age of 9 he had scarlet fever, followed by impairment of the hearing. Two years prior to the test he had urethritis. During the previous year the legs and ankles were swollen at intervals and the face and genitalia were at times edematous. Recently, he has had headaches and pain in the back and lower thoracic region. He has had no dyspnea or cyanosis.

TABLE 2.—NEPHRITIS. SUMMARY—

Case Number and Name	Date in Cal'r.	Age, Yrs.	Diagnosis	Status	Temp., C.
1. Joseph U.	3/29	19	Chronic parenchymatous, Ac. Exac.	Died 4/23	37.1
	4/ 5	..			36.7
	4/10	..			37.0
2. Lee H.	12/ 4	21	Chronic parenchymatous, Ac. Exac.	Died 1/14	36.5
	1/ 5	..			36.8
3. Edna S.	12/ 1	13	Chronic parenchymatous, Ac. Exac.	Died 5/2	37.0
4. Adam P.	1/14	26	Chronic parenchymatous, Ac. Exac.	Improved	37.1
	2/ 7	..			36.8
9. William S.	12/ 6	27	Chronic parenchymatous	Improved	36.3
5. Jack K.	4/ 4	28	Chronic interstitial	Improved	36.8
10. Isidore R.	1/24	26	Chronic interstitial, uremia	Died 1/27	37.1
6. Frank C.	2/28	19	Chronic interstitial, uremia	Died 3/27	37.1
7. John C.	2/ 9	61	Chronic interstitial	Improved	37.1
8. Mildred C.	12/10	39	Chronic interstitial (hyperthyroidism?)	Improved	....

TABLE 3.—NEPHRITIS. SUMMARY—

Case Number and Name	Date in Cal'r.	Urine				Ambard McLean Index	Blood	
		24 Hr. Volume, C.c.	Total N, Gm.	Total Cl as NaCl	Phthalein per Cent. in 2 Hrs.		Nonprotein N, Mg.	Urea, Mg.
1. Joseph U.	3/29	1,320	12.1	4.1	10	46	—	89.5
	4/ 5	946	9.1	1.8	79	47	100.0	57.4
	4/10	935	9.3	2.3	16	39	117.0	53.2
2. Lee H.	12/ 4	570	7.2	—	64	..	.....	32.0
	1/ 5	380	7.8	0.9	13	..	.....	49.0
3. Edna S.	12/ 1	.....	....	...	..	..	.....	....
4. Adam P.	1/14	1,280	7.7	4.8	27	67	39.4	20.5
	2/ 7	1,240	6.7	4.1	21	..	41.0	18.9
9. William S.	12/ 6	1,230	10.7	—	48	..	41.7	17.3
5. Jack K.	3/ 4	1,750	6.8	6.9	6	82	72.5	53.9
10. Isidore R.	1/24	.....	....	...	..	..	166.0	58.1
6. Frank C.	2/28	.....	....	...	12	49	49.7	18.9
7. John C.[4]	2/ 9	975	8.1	5.8	25	..	33.3	16.1
8. Mildred C.	12/10	.....	....	...	20	134	26.2	13.2

1. On November 24.
2. Below 47, the normal for a girl of this age.
3. Very restless.
4. 62 years old.

—OF CLINICAL DATA

Pulse	Resp. Rate	Dyspnea	Orthopnea	Periodic Resp.	Cyanosis	Edema	Blood Pressure, Syst.	Diast.
66	.....	±	—	—	—	++	175	108
55	.....	—	—	—	—	+	144	84
64	.....	±	—	—	—	+	150	94
46	15-18	+	+	—	—	+	110	80
67	.....	+	+	—	—	++	115	85
82	.....	±	++	—	—	+++	148	105
59	.....	—	—	—	—	Mod.	230	140
57	.....	—	—	—	—	—	185	120
85	20-25	±	±	..	—	++	178	90
65	.....	—	—	—	—	—	197	145
94	.....	++	—	++	±	—	155	100
88	.....	+++	++	+	..	—	220	145
60	.....	+++	++	++	+	—	230	125
104	.....	+	+	..	—	—	260	170

—OF LABORATORY DATA

Blood			CO_2 Comb. Power, Volume per Cent.	Calories per Sq. M. per Hour	Variation from Average Normal Lin.	Calories per Kg.	R. Q.
Creatinin, Mg.	Total Chlorids, Mg.	CO_2 Comb. Power, Mm. Hg.					
....	0.649	..	....	45.1	+14	1.10	0.77
1.91	0.665	26	38.8	36.9	— 7	0.95	0.83
....	0.634	38	55.0	38.0	— 4	0.99	0.79
0.84[1]	0.51 [1]	47	....	34.5	—13	1.00	0.84
3.9	0.612	..	70.2	29.0	—27	0.80	0.82
....	.....	..	....	28.0	—40[2]	0.81	0.93
....	0.623	..	57.8	35.9	—10	0.95	0.80
....	0.672	..	66.2	34.4	—13	1.00	0.81
....	.....	21[3]	....	41.2	+ 4	1.07	0.78
2.6	0.740	35	52.8	41.5	+ 5	1.15	0.80
....	0.600	19[3]	42.6	40.4[7]	+ 2	....	0.82[8]
....	0.328	..	62.5	51.2[8]	+29	1.56	0.82
....	0.594	..	69.1	40.8	+10	1.09	0.78
....	0.694	..	....	47.0	+27	1.32	0.77

5. Alveolar air.
6. On January 21
7. Calculated from CO_2 of first and third periods.
8. Somewhat restless throughout.

Physical Examination.—A somewhat undernourished young man with marked edema of the whole body, including face and genitalia. The heart is enlarged, the left border of dulness being 12.5 cm. to the left of the median line; the right border, 6 cm. to the right. At the bases of the lungs there is dulness and diminished resonance and breath sounds. There is some fluid in the abdomen.

The urine was acid; specific gravity 1.018 to 1.022; glucose absent; albumin present in large amounts, with many hyaline and granular casts and many red blood cells. Wassermann weakly positive.

December 3, a note says: "Patient lying flat in bed in no distress. Hands are blue; face neither cyanotic nor edematous. Heart sounds of good quality; no murmurs. Second sound is reduplicated; second aortic sound much accentuated. Lungs: Dulness at bases extends on both sides to within three finger-breadths of scapulae. There are a few coarse râles at the left base. Abdomen much distended and dull in right flank. No shifting dulness or fluid wave. There is marked edema of body wall from costal margin downward, and of legs and feet, and slight edema of thighs and genitalia." The phthalein test was 48 per cent. December 3. Blood pressure: 160 mm. systolic; 95 mm. diastolic. Patient was in the calorimeter December 6.

December 6, before he was put in the calorimeter, the temperature began to rise and continued irregular, reaching 103 F.; pulse 74 to 100; respirations 18 to 28. The patient developed a cough and the lungs showed many râles but no consolidation. December 8 the alveolar CO_2 was 31 mm. Hg. December 13 the febrile attack ended and patient improved steadily, but on February 4, when he was discharged, he still complained of swelling of the ankles and slight headache. The table of clinical data (Table 6), December 4 to 6, shows the urine volume 800 to 1,300 c.c., with 8 to 11 gm. nitrogen.

CASE 5.—Jack K., aged 28, baker. Admitted Feb. 15, 1916; discharged improved; chronic interstitial nephritis.

History.—At the age of 7 the patient had diphtheria. In 1901, while in the army, he had malaria. He has had frequent sore throats and in 1912 had rheumatic fever following tonsillitis. The same year he had urethritis. He was formerly a heavy drinker.

In August, 1914, he began to have pain in the head and lumbar region, epistaxis, vomiting, dizziness, edema of legs, weakness and frequency of urination. He was in the hospital for a long time, being discharged only two months before entrance into Bellevue. Feb. 12, 1916, he had nosebleed, occipital headache and dizziness. Things got black before his eyes. February 15, the day of admission, he noticed edema of the legs. He has been passing urine three to five times at night and has lost 8 pounds in one month. He has had no night sweats or cough.

Physical Examination.—A well developed and well nourished man of rather sullen demeanor. He is not dyspneic or cyanotic and there is only slight edema of the feet. Heart: Left border of dulness in the fifth space is 12.5 cm. from the median line; right border, 4 cm. to the right of median line. Radial arteries are hardened. Lungs are clear. Eyes: Fundi show slight haziness of disk outline and of vessels.

March 4 the patient was in the calorimeter. His condition was practically unchanged except that the edema had disappeared.

His urine was acid; specific gravity 1.010 to 1.012 on repeated examinations and in two-hour day and night specimens. Glucose was absent. Albumin was present in a heavy cloud, with casts, a few leukocytes, but no red blood cells. The Wassermann test on the blood was negative.

The blood pressure was, systolic, between 214 and 197; diastolic, between 96 and 145.

Phthalein Tests: February 19, 13 per cent.; March 3, 8 per cent.

Blood: February 23, nonprotein nitrogen 90.7 mg. March 3, nonprotein nitrogen 72.5 mg.; urea nitrogen, 53.9 mg.; creatinin, 2.6 mg.; chlorids, 0.740 per cent.; McLean index, 82. March 2, CO_2 combining capacity of plasma, 53 Vols. per cent.

CASE 10.—Isidore R., aged 26, pedler, Austrian Hebrew. Admitted Jan. 15, 1916; died Jan. 27, 1916; chronic interstitial nephritis; uremia.

History.—At the age of 9 years the patient had pneumonia; at 22 years, urethritis. In April, 1915, following exposure, he noticed swelling of ankles and face. Two months later the abdomen became swollen and he had anorexia and gastric distress. He went to the Michael Reese Hospital in Chicago, where he was told his blood pressure was 160 mm. He was treated with hot air baths, the ascites disappeared, and he was discharged in three months. Three weeks later the symptoms returned and he entered Mount Sinai Hospital, New York, where he was told his blood pressure was 200 to 210 mm. He left early in December and on December 21 entered Bellevue. Here his phthalein excretion, December 29, was 10 per cent. in two hours. He was transferred to the Metropolitan Hospital, but left after a few days. Previous to his second admission to Bellevue, Jan. 15, 1916, he suffered from dyspnea, edema, headache, oliguria, nausea and vomiting. The cause of his frequent changes of hospital was evidently his restless, insubordinate disposition.

Physical Examination.—January 20: A well nourished man in great distress; very pale; lying on two pillows, gasping for air, with marked sighing, deep respirations every five or six breaths. His mucous membranes were pale, his tongue coated, his pupils large and reacting sluggishly to light. Heart: Left border of dulness in the fifth space 1 cm. outside the nipple line; right border, 3 cm. from median line. The sounds are very short and snapping, with a true gallop rhythm. The lungs are clear. The abdomen is tense and tympanitic, with no dulness and no tenderness. There is no edema. The fundi show an albuminuric retinitis.

The urine, January 17, was acid; specific gravity 1.018; no glucose; albumin present in large amount; no casts seen and no red blood cells. January 19 the CO_2 combining capacity of the plasma was, in terms of alveolar CO_2, only 17 mm. Hg; January 21, only 19 mm. Since he refused all medication by mouth, he was given intravenously 400 c.c. of a 5 per cent. solution of sodium bicarbonate at 8 p. m., January 21. Half an hour later he had a chill and the pulse became very rapid. Next day the respirations, which had been rapid, shallow and periodic, became normal. The CO_2 capacity rose to 37 mm. Hg. He was brighter mentally, though still apathetic. A marked diarrhea developed. On the 23d, a pericardial rub was heard and the patient became more stuporous. He was in the calorimeter January 24. On the 27th he died. No necropsy could be obtained.

January 15 to 19 the temperature was 99 to 101; pulse 88 to 96; respirations 20 to 24; stools, one a day. January 20 to 27 the temperature was 100 to 101; pulse 92 to 110; respirations 12 to 36; stools, five to ten a day. The blood examinations were as follows:

January 20, nonprotein nitrogen, 103 mg.; chlorids 0.609 per cent. January 22, nonprotein nitrogen, 101 mg.; chlorids, 0.572 per cent. January 24, nonprotein nitrogen, 165 mg.; urea nitrogen, 68 mg.; chlorids, 0.609 per cent.

The CO_2 combining capacity of the blood plasma in volumes per cent. was as follows: January 19, 25; January 20, 29; January 21, 28; January 22, 55; (after bicarbonate) January 23, 53; January 24, 44; January 26, 51; January 27, 44.

The systolic and diastolic blood pressures were:

	Systolic, Mm.	Diastolic, Mm.
January 18	210	110
January 21	183	110
January 22	153	88
January 23	158	116
January 24	155	100

The patient took very small amounts of food and was incontinent so much of the time that it was impossible to collect twenty-four-hour specimens of urine.

TABLE 4.—NEPHRITIS—

Case Number Name and Date	Temperature Max.	Temperature Min.	Food Total Calories	Food Carbohydrate, Gm.	Food Fat, Gm.	Food N., Gm.	Urine N., Gm.	Excreta N.,[1] Gm.
Case 1 Joseph U. 3/29/16	99.4	97.8	1,081	145	42	3.9	12.1	12.5
3/30/16	99.0	97.4	1,287	176	49	4.4	11.1	11.6
3/31/16	98.8	97.8	1,651	225	54	4.9	13.2	13.7
4/ 1/16	Normal		1,554	215	59	5.0	11.3	11.8
4/ 2/16	Normal		1,562	213	59	5.2	11.4	11.9
4/ 3/16	Normal		1,579	216	61	5.1	9.6	11.1
4/ 4/16	Normal		1,455	207	52	4.8	9.7	10.1
4/ 5/16	Normal		1,200	164	53[2]	5.4	9.1	9.6
4/ 6/16	Normal		1,712	226	64	7.4	9.8	10.5
4/ 7/16	Normal		1,474	207	54	4.9	9.5	10.0
4/ 8/16	98.6	97.0	1,673	228	56	5.0	9.2	9.7
4/ 9/16	Normal		1,433	197	55	5.0	9.3	9.8
4/10/16	Normal		1,375	186	51	5.2	9.3	9.9
4/11/16	105.0	99.4	1,252	182	42	4.4	11.2	11.6
4/12/16	104.8	100.4	0[2]	0	0	0	7.9[3]	7.8
4/13/16	102.8	99.6	609	31	45	2.6	4.7[4]	5.0
4/14/16	103.8	100.6	0[2]	0	0	0	2.4[5]	2.4
4/15/16	101.4	98.8	672	61	38	2.8	1.1	2.4
4/16/16	Normal		916	116	40	2.7	2.0	2.3
4/17/16	Normal		830	88	42	3.3	2.6	2.9
4/18/16	Normal		930	88	49	4.3	2.8	3.2
4/19/16	Normal		908	117	38	2.9	3.2	3.5
4/20/16	Normal		602	122	13	1.2	6.5	6.6
4/21/16	Normal		916	149	27	2.1	6.5	6.7
Case 6 Frank C. 2/27/16	Normal		980	124	43	3.2	15.6	15.9
2/28/16	Normal		664	60	26	2.1	11.9	12.2
3/24/16	Normal		1,687	220	60	4.2	17.5	17.9
3/25/16	Normal		792	108	22	1.8	15.7	15.9

1. Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.
2. Vomited.
3. 26 hours 20 minutes.
4. 21 hours 40 minutes.
5. 24 hours 10 minutes.

—Clinical Data

Nitrogen Balance, Gm.	Body Weight, Kg.	Urine Volume, C.c.	Calories per Kg.	Fluid Intake, C.c.	NaCl Intake, Gm.	Urine NaCl, Gm.	Blood Pressure, Syst.	Blood Pressure, Diast.
−8.6	75.7	1,520	14	1,020	1.34	4.08	175	108
−7.1	74.7	1,470	16	1,235	1.10	4.78	165	113
−8.8	73.5	1,682	21	1,470	1.44	4.91	168	110
−6.8	72.9	1,340	21	1,470	1.27	3.84		
−6.7	72.1	1,230	21	1,420	1.39	3.36		
−6.1	71.2	1,090	22	2,050	1.34	3.17		
−5.4	71.4	1,030	20	1,970	1.69	2.19		
−4.3	70.8	946	17	1,380	2.09	1.84	144	84
−3.1	71.4	1,056	24	1,680	2.09	2.03		
−5.0	71.8	995	20	1,400	1.31	1.66		
−4.7	70.8	1,000	23	1,725	1.77	1.66		
−4.8	71.3	1,040	20	2,020	1.74	1.84		
−4.6	70.6	935	19	2,150	1.97	2.30		
−7.2	72.1	1,090	17	2,875	1.38	1.18	150	94
−7.8	....	750[2]	0	1,360	0	0.52		
−2.4	71.2	480[4]	8	1,380	0.88	0.52	134	90
−2.4	....	250[5]	0	2,275	0	0.09		
+0.4	....	160	9	1,000	0.85	0.22		
+0.4	....	290	13	820	0.92	0.40	150	90
+0.4	71.0	350	11	1,005	1.02	0.40		
+1.1	71.0	300	12	1,515	1.54	0.23		
+0.5	70.9	420	12	1,200	1.05	0.31		
−5.4	71.1	400	9	760	0.52	0.45		
−4.6	70.9	380	12	950	0.77	0.36		
−12.7	51.0	2,340	19	2,010	....	4.03	220	145
−10.0	50.2	2,292	13	2,360	0.70	1.86		
−13.7	49.4	4,260	34	1,000	1.18	7.72		
−14.1	48.7	2,930	16	3,270	0.43	4.82		

TABLE 5.—NEPHRITIS.—

Case Number, Name and Date	Food			Food N., Gm.	Urine N., Gm.	Excreta N.,[1] Gm.	Nitrogen Balance, Gm.
	Total Calories	Carbohydrate, Gm.	Fat, Gm.				
Case 4 Adam P.[2]	.....	...	..	...	....	....	.....
1/13/16	1,608	153	79	4.6	11.0	11.5	−6.9
1/14/16	1,606	145	95	4.6	7.7	8.2	−3.6
1/15/16	1,627	208	72	5.0	9.3	9.8	−4.8
1/16/16	1,609	208	72	4.4	8.1	8.5	−4.1
1/22/16	1,174	154	47	4.1	7.6	8.0	−4.0
1/23/16	1,464	204	58	5.2	8.2	8.7	−3.5
1/24/16	1,345	175	58	5.1	7.2	7.7	−2.6
1/25/16	1,616	224	61	5.1	7.7	8.2	−3.1
1/26/16	1,595	205	66	5.5	7.9	8.4	−2.9
1/27/16	1,391	186	54	5.0	6.6	7.1	−1.1
1/28/16	1,486	214	51	5.3	6.9	7.4	−2.1
1/29/16	1,434	179	62	4.8	6.0	6.5	−1.7
1/30/16	1,577	226	57	4.6	7.0	7.5	−2.9
1/31/16	1,601	216	63	5.3	7.9	8.4	−3.2
2/ 1/16	1,423	204	52	4.2	6.4	6.8	−2.6
2/ 2/16	1,518	202	60	5.0	6.2	6.7	−2.7
2/ 3/16	1,634	225	62	4.9	6.7[3]	7.2	−2.3
2/ 4/16	1,488	211	54	4.8	6.5[4]	7.0	−2.2
2/ 5/16	1,569	225	56	4.9	5.6[5]	6.1	−1.2
2/ 6/16	1,477	194	60	4.9	6.7[6]	7.2	−2.3
2/ 7/16	1,321	181	48	5.2	6.7	7.2	−2.0
2/ 8/16	1,558	221	56	4.8	6.6	7.0	−2.2
2/ 9/16	1,529	212	57	4.8	6.5	7.0	−2.1
2/10/16	2,153	195	108	15.2	7.0	8.5	+6.7
2/11/16	2,138	192	105	14.6	10.4	11.9	+2.7
2/12/16	2,024	204	87	14.9	11.1[7]	12.6	+2.3
2/13/16	2,029	199	86	15.1	12.2[8]	13.7	+1.4
2/14/16	2,010	191	90	15.2	13.7	15.1	+0.1

1. Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.
2. Temperature normal.
3. 25 hours 15 minutes.
4. 22 hours 25 minutes.
5. 23 hours 25 minutes.
6. 24 hours 55 minutes.
7. 22 hours 20 minutes.
8. 25 hours 35 minutes.

—Clinical Data

Body Weight, Kg.	Urine Volume, C.c.	Calories per Kg.	Fluid Intake, C.c.	NaCl Intake, Gm.	Urine NaCl, Gm.	Blood Pressure Syst.	Blood Pressure Diast.
.....	.....	..	.....	....	....	230	140
61.4	1,590	26	.....	2.57	7.48	226	200
60.6	1,280	26	.....	1.30	4.78		
60.3	1,460	26	1,392	1.68	7.77		
58.3	1,040	27	1,518	0.64	5.39		
54.6	960	22	830	1.18	6.28		
54.6	1,460	27	1,220	1.22	13.34		
54.3	975	25	960	1.39	3.61		
53.7	940	30	810	1.99	3.76		
58.8	1,270	29	1,215	2.00	6.23		
53.7	900	26	820	1.24	3.83		
53.2	1,010	27	1,255	1.68	3.15		
53.6	930	26	1,050	1.71	2.02		
53.9	930	29	1,550	1.34	1.86		
54.8	1,140	29	1,314	2.12	2.30		
54.7	1,410	26	1,540	1 48	1.62	205	130
55.0	1,180	27	1,175	1.54			
55.1	960	29	1,085	2.01	1.91	195	120
54.8	1,340	27	970	1.36	3.17		
53.6	1,280	29	995	1.87	2.88		
53.3	1,360	27	800	1.38	5.65		
52.5	1,337	25	1,080	1.36	4.08	185	120
52.6	1,425	29	1,185	1.66	3.88		
52.4	1,200	29	925	1.40	4.79		
51.6	840	41	1,000	3.39	4.70		
51.7	1,060	41	1,290	3.23	3.64	193	128
51.6	1,000	39	1,040	2.96	5.55		
51.5	1,040	39	1,060	2.90	4.61		
51.7	1,120	38	1,160	2.80	4.98		

TABLE 6.—NEPHRITIS.—

Case Number Name and Date	Temperature Max.	Temperature Min.	Food Total Calories	Food Carbohydrate, Gm.	Food Fat, Gm.	Food N., Gm.	Urine N., Gm.	Excreta N.,[1] Gm.
Case 2 Lee H. 12/ 4/15	98.0	97.6	1,152	116	56	6.2	7.2	7.8
1/ 5/16	100.6	98.6	1,146	136	51	4.6	7.8	8.3
1/ 6/16	101.8	98.2	447	32	27	3.2	6.8[2]	7.1
1/ 7/16	102.0	98.6	296	14	20	2.5	16.8[3]	17.1
1/ 8/16	103.4	99.2	477	45	20	4.0	16.3	16.7
1/ 9/16	103.0	99.6	544	49	27	3.9	14.0	15.0
1/10/16	102.6	100.6	664	68	31	4.0	14.1	14.5
1/11/16	102.4	100.6	142	12	8	0.7	11.3	12.0
1/12/16	102.0	98.6	412	46	16	2.8	11.1	11.3
Case 9 William S. 12/4/15	....	....	1,266	140	55	7.2	9.6	10.3
12/5/15	99.2	97.0	1,180	141	42	5.6	7.6	8.4
12/6/15	103.0	99.8	1,470	144	69	9.4	11.1[4]	12.0
Case 7 John C. 2/ 8/16	Normal							
2/ 9/16	Normal		1,415	180	57	4.4	8.1	8.5
2/10/16	Normal		2,009	285	76	5.3	6.1	6.6
2/11/16	Normal		1,959	269	78	5.2	5.9	6.4
Case 5 Jack K. 9/4/16	.....		1,569	204	66	4.7	6.8	7.3

1. Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.
2. 22 hours.
3. 25 hours.
4. 22 hours 25 minutes.

CASE 6.—Frank C., aged 19, born in Italy. Admitted Feb. 23, 1916; died March 27, 1916; chronic interstitial nephritis; uremia.

History.—No cause of nephritis was found. He says he has always been well and has been a very moderate user of alcohol. For many years he has had nocturia; for two and a half months dimness of vision; for two days, severe frontal headache and scanty urine; for one day, nausea and vomiting. He has had no edema.

Physical Examination.—Patient is well developed and well nourished. He is dyspneic, orthopneic, pale; his eyes have a vacant stare; and he is evidently in pain. Breath urinous. He has no edema. Heart: Left border of dulness in the fifth space 1 cm. outside the nipple line; right border at the sternal margin; no murmurs; second aortic sound markedly accentuated. Arteries not markedly sclerosed. Fundi show marked albuminuric retinitis with hemorrhages. He cannot count fingers at 2 feet.

The urine contained a large amount of albumin, many hyaline and granular casts and a few red blood cells. The Wassermann reaction was very faintly positive.

February 24 he had a spastic convulsion lasting forty-five minutes.

—Clinical Data

Nitrogen Balance, Gm.	Body Weight, Kg.	Urine Volume, C.c.	Calories per Kg.	Fluid Intake, C.c.	NaCl Intake, Gm.	Urine NaCl, Gm.	Blood Pressure, Syst.	Diast.
−1.5	55.1	570	21	.....	4.30	....	110	80
−3.7	....	260	..	1,278	2.20	0.85	115	85
−3.4	61.5	240	7	980	0.23	Trace		
−14.6	....	600	..	1,160	0.97	Trace		
−12.7	60.7	940	8	1,140	0.56	Trace		
−12.0	60.2	940+	9	745	0.92	Trace		
−10.5	59.1	900+	11	880	1.56	Trace		
−11.3	59.1	640+	2	885	0.39	Trace		
−9.0	55.9	616	7	720	0.65	Trace		
−3.1	....	1,360	..	.....	4.24			
−0.4	64.1	780	18	.....	7.72	....	155	120
−2.6	64.2	1,278	21	.....	4.40	....	178	90
−4.1	70.0	975	22	955	1.55	5.75	230	125
−1.3	70.1	480	29	850	2.10	1.92		
−0.5	69.3	420	28	975	1.89	2.06	226	130
−8.6	58.5	1,750	26	870	3.23	6.92	197	145

The patient was in the calorimeter February 28. He was irrational and very restless, sitting up in the bed at frequent intervals. His condition had not changed much since admission and he still had headache, but he was passing urine freely, 2,300 to 4,300 c.c. per diem, containing 12 to 17 gm. nitrogen and 2 to 8 gm. sodium chlorid. His breath was not so urinous. The blood pressure was 250 mm. systolic; 130 mm. diastolic.

For a time he improved. March 15 his hemoglobin was 56 per cent.; red blood cells, 3,350,000. March 22 the nonprotein nitrogen of the blood was 46 mg.; creatinin, 1 mg. In the spinal fluid the nonprotein nitrogen was 32 mg.; urea, 17 mg. Blood pressure: 220 mm. systolic; 178 mm. diastolic.

March 21 he began to have headache and nausea once more. March 22 he had a convulsion. After this he became blind, grew more toxic, with marked headaches, and on March 27 died. No necropsy was obtained.

February 28 the urine was collected as follows:

Time of Voiding	Volume, C.c.	Specific Gravity
9:00 a. m.....	410	1.010
2:30 p. m.....	425	1.015
5:20 p. m.....	400	1.010
9:10 p. m.....	300	1.010
4:00 a. m.....	600	1.012
6:30 a. m.....	280	1.010

February 28, McLean index 79. CO_2 combining capacity of the plasma in volume per cent., February 24, 66; February 28, 64.

Case 7.—John C., aged 61, watchman. Admitted Feb. 8, 1916; transferred to City Hospital Feb. 18, 1916, improved; chronic interstitial nephritis.

History.—Thirty-five years prior to test he had urethritis and probably lues. Six years prior he had rheumatic pains in the left shoulder. He has been an excessive pipe smoker but a moderate user of alcohol. In spite of his 61 years he still had the sexual vigor of a young man.

Two years prior to test his joints ached and he was told that his blood pressure was 288 mm. For the five months previous to examination he had been unable to work on account of failing eyesight. He has been dyspneic on climbing two flights of stairs. At times he has severe frontal headaches, dizziness and occasionally loses control of his tongue and becomes aphasic. He has marked frequency of urination, six to eight times in the day, four or more times at night.

Physical Examination.—Well nourished; looks younger than his age. His respirations are deep and regular. He is orthopneic but not cyanotic or edematous. The teeth are in very bad condition. Heart: Apex beat in the sixth space 15 cm. from the median line; second aortic sound much accentuated. There is a large, deep scar on the penis.

Urine: February 8 the phthalein output was 25 per cent. in two hours. February 9 to 12 the daily urine volume was 400 to 1,000 c.c.; nitrogen, 6 to 8 gm.; sodium chlorid 2 to 6 gm. His temperature was normal; pulse 60 to 88; respiration 14 to 22. The blood pressure on two examinations was 285 and 236 mm. systolic; 165 and 130 mm. diastolic. February 8 the McLean index was 136 and the CO_2 combining power of the plasma was 69 volumes per cent.

Case 8.—Mildred C., aged 39, milliner, born in England, single. Admitted Nov. 23, 1915; discharged improved, Jan. 6, 1916. Chronic interstitial nephritis; uremia; hyperthyroidism (?).

History.—Three years prior to admission she had diphtheria. In August, 1915, while on a street car, she began to suffer from headache and vomiting and was brought to Bellevue, where she remained unconscious for four days, and was discharged two weeks later. At this time the urine contained much albumin and many hyaline and granular casts. The Wassermann reaction was strongly positive.

As long as she can remember she has had severe headaches, with nausea and vomiting. These come about every month but are not related to the menses, which are normal. Her appetite is fair, bowels constipated. For one year she has had marked nocturia.

Following her first stay in Bellevue she went back to work. For a week she has had a severe headache. She has had no dyspnea and no edema.

Physical Examination.—November 23: A thin, nervous woman who looks chronically ill. She is slightly dyspneic and orthopneic. There is moderate exophthalmos but no von Graefe's sign, no goiter, no tremor and only slight tachycardia. Heart: Left border of cardiac dulness is 12.5 cm. from the midsternal line; right border, at right sternal margin; the second aortic sound is accentuated; in the aortic region there is a thrill and a systolic murmur. The lungs are normal. The liver edge, spleen and right kidney are palpable. The knee jerks are exaggerated. Ophthalmoscopic examination, negative.

The urine was acid; specific gravity 1.010 to 1.018; glucose absent; albumin present in large amount; a few granular casts were found but no red blood cells. The blood count showed:

Red blood cells	5,080,000
Leukocytes	7,200
Differential, normal	

The patient was put on a somewhat restricted diet and given chloral, 5 grains, and potassium iodid, 5 grains, every day except December 10, when she was in the calorimeter. She improved steadily and was able to go back to work January 6.

The temperature was normal; pulse, 85 to 100; respiration, 20 to 22. The systolic and diastolic blood pressures were as follows:

	Systolic, Mm.	Diastolic, Mm.
November 23	265	190
December 9	260	170
January 5	250	150

Phthalein test, December 1, first hour, 10 per cent.

November 30 the blood analysis was as follows:

Sugar	105.0	mg.
Chlorids	0.54	per cent.
Urea nitrogen	25.0	mg.
Ammonia nitrogen	3.2	mg.
Uric acid	2.6	mg.
Creatinin	2.0	mg.
Corpuscular volume	36.0	per cent.

December 10 the McLean index was 134.

Feb. 13, 1916, the patient was admitted to Bellevue once more. She had a severe headache the day before admission, followed by a general convulsion. The blood pressure was 240 mm. systolic; 128 mm. diastolic. A few days later she left the hospital in fair condition.

477 First Avenue.

CLINICAL CALORIMETRY

TWENTY-THIRD PAPER

THE EFFECT OF ROENTGEN-RAY AND RADIUM THERAPY ON THE METABOLISM OF A PATIENT WITH LYMPHATIC LEUKEMIA*

JAMES B. MURPHY, M.D.
NEW YORK

J. H. MEANS, M.D.†
BOSTON

AND

J. C. AUB, M.D.
NEW YORK

In this paper there will be presented the results of calorimetric observations made in a case of chronic lymphatic leukemia, both before and after vigorous Roentgen-ray therapy, and also after exposure to radium. The basal metabolism in leukemia will be discussed and the effect of irradiation thereon.

The literature contains but few observations of this sort. Those by Grafe,[1] Magnus-Levy,[2] Kraus,[3] and Bohland[4] being the only ones that we have found suitable for comparison with cur own case.

By referring to Table 1, in which the experiments of these several authors are collected,[5] it will be seen that in both forms of leukemia there is invariably a marked rise in the basal metabolism expressed in terms of body surface area. This is found in both types about equally, the average increase over the normal in eight cases of lymphatic leukemia being 52 per cent., and in five of the myelogenous type, 44 per cent.[6]

The cause of the increase is uncertain; Grafe believed it to be due to the active metabolism of the large numbers of premature white

---

* Submitted for publication Dec. 19, 1916.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

† Henry P. Walcott Fellow in Clinical Medicine, Harvard University.

1. Grafe, E.: Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, Deutsch. Arch. f. klin. Med., 1911, **102,** 406.

2. Magnus-Levy, A.: Ueber den Stoffwechsel bei acuter und chronischer Leukämie, Virchows Arch. f. path. Anat., 1898, **152,** 107.

3. Kraus, F.: Ueber den Einfluss von Krankheiten, besonders von anämischen Zuständen, auf den respiratorischen Gaswechsel, Ztschr. f. klin. Med., 1893, **22,** 449.

4. Bohland, K.: Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, Berl. klin. Wchnschr., 1893, **30,** 417.

5. A more extended form of this table will be found in Paper 15 of this series, THE ARCHIVES INT. MED., 1916, **17,** 974.

6. In this discussion the patients S. W. of Kraus and H. of Bohland were omitted, there being some uncertainty as to which type of leukemia they belonged.

blood cells. He based this belief on observations made on the metabolism of leukemic blood which he carried out by several methods, chiefly by Bohr's blood gas pump or the Haldane-Barcroft blood gas analysis apparatus. Calculating from such experiments, he found that in individual cases the oxygen demand of the total number of leukocytes in the body might form as much as 10 per cent. of the patient's total oxygen requirement.

The intensity of the rise in basal metabolism, Grafe found, ran parallel with the clinical severity of the disease.

The total nitrogen metabolism has been studied by numerous investigators. Such observations as those of von Noorden,[7] Magnus-Levy,[8] Taylor,[8] Musser and Edsall,[9] Edsall,[10] Goodall,[11] Stejskal and Erben,[12] Döri[13] and of Cavina[14] seem to show fairly definitely that there is, in chronic leukemia, no increase in nitrogenous metabolism at all comparable with that in the respiratory metabolism. There is either a slight retention, a slight loss, or a balance. In acute leukemia, on the other hand, as shown by Magnus-Levy's and Edsall's cases, there is an enormous increase in protein metabolism. Edsall's patient had a negative nitrogen balance of 22.28 gm. a day while on a nitrogen intake of 7.25 gm.!

A marked increase in the uric acid output has been found by a number of observers. One of Magnus-Levy's cases, on a low food intake, excreted 12.2 gm. of uric acid. Wende[15] reports a case of lymphatic leukemia with a uric acid excretion of 5 gm. The case of acute leukemia of Edsall and the two cases of chronic leukemia of Musser and Edsall all showed an increased uric acid output. Lossen and Morawitz[16] also report two cases with high uric acid elimination.

---

7. Von Noorden, C.: Lehrbuch der Pathologie des Stoffwechsels, Berlin, 1893, p. 349.

8. Taylor, A. E.: Contributions from the William Pepper Laboratory of Clinical Medicine, 1900, No. 2, p. 148.

9. Musser, J. H., and Edsall, D. L.: Study of the Metabolism in Leukemia, Under the Influence of the X-Ray, Tr. Assn. Am. Phys., 1905, **20,** 294.

10. Edsall, D. L.: Case of Acute Leukemia, with Some Striking Clinical Features, Tr. Assn. Am. Phys., 1905, **20,** 279.

11. Goodall, H. W.: Nitrogenous Metabolism in a Case of Chronic Myelogenous Leukemia, Boston Med. and Surg. Jour., 1914, **170,** 789.

12. Stejskal, C. v., and Erben, F.: Stoffwechselversuch bei lymphatischer und lienalmyelogener Leukämie, Ztschr. f. klin. Med., 1900, **39,** 151.

13. Döri, B.: Stoffwechseluntersuchungen bei einer mit Benzol behandelten chronischen leukämischen Myelose, Wien klin. Wchnschr., 1913, **26,** 2034.

14. Cavina, G.: Untersuchungen über den Stoffwechsel bei der lymphatischen Leukämie während der Röntgenbestrahlung, Deutsch. Arch. f. klin. Med., 1913, **110,** 585.

15. Wende, G. W.: Case of Lymphatic Leukemia, Am. Jour. Med. Sc., 1901, **122,** 836.

16. Lossen, J., and Morawitz, P.: Chemische und histologische Untersuchungen an bestrahlten Leukämikern, Deutsch. Arch. f. klin. Med., 1905, **83,** 288.

TABLE 1.—BASAL METABOLISM IN CASES OF—

Observer	Type	Patient	Calories per Square Meter per Hour (Mesh)
Grafe, E.	Lymphatic	T. S. 1a	68.7
		T. S. 1b	52.0
		T. S. 1c	48.7
	Lymphatic	G. K. 2	36.8
	Lymphatic	C. L. 3a	44.5
		C. L. 3b	46.9
	Lymphatic	M. T. 4	65.0
	Lymphatic	M. D. 5	49.8
	Myelogenous	F. H. 6	53.2
	Myelogenous	M. H. 7	49.8
	Myelogenous	H. B. 8	42.3
Magnus-Levy	Lymphatic	J.	45.1
Kraus, F.	Splenomyelogenous	M. B.	48.7
		M. B.	46.4
		M. B.	45.8
	Splenomyelogenous	W. K.	47.8
		W. K.	46.7
		W. K.	49.4
	Lienalis	S. W.	49.7
		S. W.	49.2
Bohland, K.	Lienalis	H.	51.8
		H.	57.8
		H.	56.7
		H.	54.8
	Lymphatic	B.	55.3
		B.	42.1
		B.	42.9
	Lymphatic and lienalis	L.	48.0
		L.	43.7
		L.	42.9
		L.	59.0
		L.	47.2

* For normal averages those given in Paper 12 of this series (Gephart and Du Bois, THE ARCHIVES INT. MED., 1916, 17, 913) were used

—Leukemia Collected from the Literature

Per Cent. Above or Below Average Normal*	Total Leukocytes	Per Cent. Polymorphonuclears	Per Cent. Leukocytes	Total Red Cells	Per Cent. Hemoglobin
+123	820,000	10	89	3,600,000	40
+69	205,000	10	89		
+58	200,000	5	95	2,400,000	30
+19	40,000	28	72	4,800,000	90
+55	180,000	4	96		
+63	165,000	2	98	3,640,000	75
+87	32,000	12	87	3,800,000	70 to 75
+62	170,000	2	98	3,800,000	80
+53	140,000	95	5	4,700,000	60
+54	180,000	95	5	2,600,000	55
+22	230,000	98	2	.....	75
+30					
+58	450,000	..	..	2,800,000	50
+51					
+49					
+38	230,000	..	..	2,400,000	45
+35					
+42					
+54	345,000 to 425,000	..	..	2,990,000 to 2,720,000	50 to 45
+52		..	..		
+60	Ratio of Whites to Reds = 1:5				
+79					
+76					
+70					
+59	Ratio of Whites to Reds = 1:50				
+21					
+24					
+38	Ratio of Whites to Reds = 1:10				
+26					
+24					
+70					
+36					

In Goodall's case there was a high endogenous uric acid elmination, but this showed marked variation which had no relation to the total nitrogen or to the apparent leukocyte destruction. Goodall concluded that the destructive process might be carried beyond the uric acid stage, and that, also, retention of uric acid might occur for the purpose of new leukocyte formation. Other writers, among them Stejskal and Erben,[12] and Rzentkowski,[17] have found no increase in the uric acid output in chronic leukemia. The latter not only failed to find any increase in the endogenous uric acid elimination, but also on feeding meat, Liebig's extract, or uric acid, failed to get an increase in the exogenous elimination. This suggested that the process of uricolysis was increased over the normal.

Folin and Denis[18] have found that the blood uric acid is markedly increased in leukemia.

A retention of phosphates in leukemia has been found by several writers, Moraczewski,[19] Stejskal and Erben,[12] and Musser and Edsall.[9] The latter believe this retention to be due to the rapid building of leukemic tissue, a tissue especially rich in phosphorus.

Stejskal and Erben found a loss of calcium in their case of lymphatic leukemia.

There seems to be, therefore, plenty of evidence to show that a profound change in the general metabolism may occur in leukemia. Since this is so, and since Roentgen and radium therapy have been used very extensively of late in both types of chronic leukemia, it seemed important to determine the effect of such forms of treatment on the leukemic's basal metabolism.

That the Roentgen ray is capable of producing a change in the metabolism in normal individuals is shown by the experiments of Linser and Sick[20] who found an increase in uric acid and purin bases and a decrease in the leukocytes of the blood after irradiation. Baermann and Linser[21] also found a rise in the total nitrogen. Benjamin and von Reuss,[22] in a normal dog after a single very intense

17. Rzentkowski, K.: Untersuchungen über den Purinstoffwechsel in einem Falle von lymphatischer Leukämie, Zentralbl. f. Biochem. u. Biophysik, 1911, **11,** 717.

18. Folin, O., and Denis, W.: On Uric Acid, Urea and Total Nonprotein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, **14,** 29.

19. Moraczewski, W. v.: Stoffwechselversuche bei Leukämie und Pseudoleukämie, Virchows Arch. f. path. Anat., 1898, **151,** 22.

20. Linser, P., and Sick, K.: Ueber das Verhalten der Harnsäure und Purinbasen im Urin und Blut bei Roentgenbestrahlungen, Deutsch. Arch. f. klin. Med., 1906-1907, **89,** 413.

21. Baermann, G., and Linser, P.: Ueber die lokale und allgemeine Wirkung der Röntgenstrahlen, München. med. Wchnschr., 1904, **51,** 996.

22. Benjamin, E., and v. Reuss, A.: Roentgenstrahlen u. Stoffwechsel, München. med. Wchnschr., 1906, **53,** 1862.

exposure, found a slight rise in the total nitrogen, on a fixed intake, lasting several days, and after the second day an increase in phosphorous pentoxid.

A number of writers, among others Ellis,[23] Morris,[24] Heineke,[25] Helber and Linser,[26] Belot[27] and Harvey[28] have described the histologic action of the Roentgen ray on normal tissues. In general, the effect seems to be a destructive action on the entire hematopoietic system. Such organs as the spleen show a diminution in size and degeneration of the parenchyma after irradiation. The action seems to be particularly active in the case of white blood cells, especially those of the lymphocyte series. The white cells, both in the circulation and in the blood forming organs, are attacked. The nucleus is fragmented first, and after this there is a lysis of the entire cell.

We have not found in the literature any observations on the effect of irradiation on the basal metabolism in normal individuals. The effect of the Roentgen ray has been studied very much more extensively in the case of the leukemic than in that of the normal individual. Since Senn,[29] in 1903, first used Roentgen therapy in leukemia, scores of papers on this subject have appeared. A very extensive bibliography up to 1911 will be found in the paper of Keymling.[30]

The effect of irradiation on the basal metabolism was studied in Grafe's case, T. S. (Table 1). The heat production per square meter per hour having been 68 calories before treatment, fell to 52 calories and later to 48 while under treatment. During this time the leukocyte count fell from 820,000 to 200,000.

The changes in the total nitrogen, uric acid and purin base elimination after Roentgen-ray treatment have been observed by numerous writers. Lossen and Morawitz,[16] in one case of myelogenous leukemia, found that the uric acid elimination, having been high during irradia-

23. Ellis, A. G.: The Pathology of the Tissue Changes Induced by the X-Ray, Am. Jour. Med. Sc., 1903, **125,** 85-96.

24. Morris, R. S.: Action of Roentgen Rays on the Blood, Am. Med., 1905, **10,** 946.

25. Heineke, H.: Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1905, **14,** 21.

26. Helber, E., and Linser, P.: Experimentelle Untersuchungen über die Einwirkung der Roentgenstrahlen auf das Blut, München. med. Wchnschr., 1905, **52,** 689.

27. Belot, J.: On the Influence of the X-Ray on the Hematopoietic Organs, Arch. Röntgen Ray, 1906, **11,** 67 and 108.

28. Harvey, W. G.: On the Pathological Effects of Röntgen Rays on Animal Tissues, Jour. Path. and Bacteriol., 1908, **12,** 549.

29. Senn, N.: Case of Splenomedullary Leukemia Successfully Treated by the Use of the Roentgen Ray, Med. Rec., New York, 1903, **64,** 281.

30. Keymling, E.: Die Röntgen-therapie der Leukämie, Ztschr. f. Röntgen u. Radiumforsch., 1911, **13,** 306, 337, 428, 453.

tion, returned to normal coincidently with the leukocyte count. In another case of the same disease they found that the uric acid remained high even after irradiation had produced an actual leukopenia. Heile[31] found an increase in both uric acid and purin bases in three cases. Königer,[32] in seven cases of chronic myelogenous leukemia, found a marked change in the uric acid elimination following irradiation. This consisted, first, in a marked increase, and later, in a reduction to a normal figure as the blood picture approached an aleukemic condition. Cavina,[14] on the other hand, found no increase either in uric acid or total nitrogen in a case of lymphatic leukemia while the patient was being treated with the Roentgen ray. The nitrogen balance was invariably positive, although the leukocyte count fell from 60,860 to 24,800.

The cases of Musser and Edsall[9] are especially interesting in this connection. In one of their cases in which the Roentgen ray had no beneficial effect clinically, it likewise had little or no effect on the nitrogenous metabolism, whereas in the other case, in which there was a marked reduction in the number of white cells and clinical improvement, there was a definite increase in uric acid and purin base output, a very striking loss of nitrogen and an increased elimination of phosphorus pentoxid.

The histologic action of the Roentgen ray seems to be essentially the same in leukemia as in normal individuals. It has been described in detail in the papers of Warthin[33] and of Aubertin and Beaujard.[34] The immediate action is that most cells of the hematopoietic organs are either destroyed at once or so damaged that they become so later. This action is especially violent on cells of the lymphatic series. In either the lymphatic or the bone marrow series, however, both young and old cells are attacked, with the result that, although the total number of white cells may be reduced to normal and the blood rendered aleukemic, nevertheless the differential count never becomes normal. Pathologic cells persist even when an absolute leukopenia has been produced. As a number of writers point out, therefore, the treatment is purely palliative, but, owing to the great reduction in the size of the spleen and the general clinical improvement, in many cases is, nevertheless, distinctly worth while.

---

31. Heile: Ueber intravitale Beeinflussung autolytischer Vorgänge im Körper, Ztschr. f. klin. Med., 1904, **55,** 508.

32. Königer, H.: Der Einfluss der Roentgenbehandlung auf den Stoffwechsel bei chronischer myeloider Leukämie, Deutsch. Arch. f. klin. Med., 1906, **87,** 31.

33. Warthin, A. S.: The Minute Changes Produced in Leukemic Tissues by Exposure to Roentgen Rays, Am. Jour. Med. Sc., 1914, **147,** 72.

34. Aubertin, C., and Beaujard, E.: Sur le mode d'action de la radiothérapie dans la leucémie myéloïde, Bull. et mém. Soc. méd. d. hôp. de Paris, Series 3, 1913, **36,** 66.

The effect of radium on the metabolism has been studied by Kikkoji[35] who found a significant increase in the basal metabolism in a case of chronic arthritis and in a normal man, but found no effect in a second case of chronic arthritis. The two cases that showed a rise in basal metabolism likewise showed an increase in total nitrogen and uric acid elimination.

Histologically, as shown by the researches of Proescher and Almquest,[36] radium has much the same action on the blood-cells and hematopoietic organs as the Roentgen ray.

Let us now sum up the various facts gathered from the literature. In the first place, there is good evidence that the basal metabolism is always increased in leukemia.

The metabolism of leukemic blood is more active than that of normal blood.

The nitrogenous balance is usually negative in acute and variable in chronic leukemia.

The endogenous uric acid elimination and the uric acid content of the blood are generally increased.

There is often a retention of phosphates.

The Roentgen ray may or may not have a profound effect on the metabolism in leukemia. When it does, this effect consists in an increased elimination of nitrogen; also of uric acid, the latter, however, returning to a normal figure as the leukocyte count approaches normal.

When the leukocyte count falls as a result of irradiation, there is some evidence to show that the basal metabolism falls coincidently.

METHODS USED

During the period that he was under observation the subject of this research, Anthony W., spent part of the time in the metabolism ward of the Sage Institute, a part at the hospital of the Rockefeller Institute, and a part at Saint Luke's Hospital, New York.

While at the Sage Institute the methods used, both those of calorimetry and the general routine, were as already described in the third and fourth papers of this series.[37] The uric acid in blood and urine

35. Kikkoji, T.: Ueber den Einfluss von Radiumemanation auf den Gesamtstoffwechsel in Organismus, Radium in Biologie und Heilkunde, 1911, **1,** 46.

36. Proescher, F., and Almquest, B. R.: Contribution on the Biological and Pathological Action of Soluble Radium Salts, with Special Reference to Its Therapeutic Value in Pernicious Anemia and Leukemia, Radium, 1914, **3,** 65.

37. Gephart, F. C., and Du Bois, E. F.: The Organization of a Small Metabolism Ward, THE ARCHIVES INT. MED., 1915, **15,** 829; The Determination of the Basal Metabolism of Normal Men and the Effect of Food, ibid., p. 835.

was determined by Benedict's[38] method. For the calorimeter experiments the steamer chair was used.

The Roentgen-ray treatments were given at the hospital of the Rockefeller Institute. The treatment used varied from that generally employed in that the whole surface of the body was exposed to a radiation of low penetration.

The radium treatments were given by Dr. Karl M. Vogel at St. Luke's Hospital. Radium was applied over the splenic region on six occasions in the months of July, August and September, 1916.

HISTORY OF CASE

History.—Anthony W., man, aged 59, single, born in Ireland, was admitted to the Sage Metabolism Ward in Bellevue Hospital April 18, 1916 (chronic lymphatic leukemia). He had been in America since 1898.

Family History.—Gout on both sides of the family; otherwise negative.

Past History.—At the age of 7 he had diphtheria and scarlet fever, which were followed by "dropsy." At 10 years he had typhoid fever. Between the ages of 18 and 25 he had rather severe attacks of migraine. When 33 years old he had pains in the left great toe which, he was told, were due to gout. Four years later he had an attack of sciatica which lasted for six months.

Present History.—Symptoms referable to the present trouble had existed for thirteen months before his admission to Bellevue Hospital (March, 1915), when he began to have intermittent attacks of severe pain in the left lower part of the abdomen. The pain was definitely localized above the crest of the ilium and in the groin. It radiated occasionally to the back and left arm. In October, 1915, he began to notice shortness of breath on slight exertion, with a slight orthopnea at night. In December, 1915, he first noticed a firm mass in the left upper quadrant. About the same time he began to have severe cramp-like contractions in the leg muscles as far as the thigh and in the muscles of the hands. They came frequently during the day, lasted two to three minutes, and were relieved by exercise. In the previous thirteen months he had lost about 50 pounds. His appetite and digestion had been good. He had been constipated and had had a moderate nocturia.

Physical Examination.—A well developed, but poorly nourished man, lying comfortably in bed. His skin, sclerae and mucous membranes are pale. The lower teeth show moderate pyorrhea. The thyroid is not enlarged. The heart is enlarged; the borders percuss 15 cm. to the left and 4 cm. to the right of the midsternal line. At the apex and along the sternal margin there is a rough systolic murmur, loudest and roughest in the third left interspace. The lungs are normal.

The spleen can be felt as a definitely outlined, firm mass, dull to percussion, filling the entire left, upper quadrant, and causing a marked bulging in the left flank. Its greatest length is 33.5 cm.; greatest width 18.5 cm. It extends from 2 cm. to the right of the midsternal line deep into the flank, from 11 cm. above the costal margin to 4 cm. below the umbilical line. In the median line, near the costal margin, are left two definite notches. The liver dulness extends from the fifth rib to the costal margin. There are a few pea-sized, soft glands posterior to the left sternomastoid muscle. There

38. Benedict, S. R., and Hitchcock, E. H.: On the Calorimetric Estimation of Uric Acid in Urine, Jour. Biol. Chem., 1915, **20,** 619. Benedict, S. R.: On the Calorimetric Determination of Uric Acid in Blood, ibid., 1915, **20,** 629.

are larger masses in both axillae and a mass the size of an almond in the left groin. Blood pressure, 142 mm. systolic; 105 mm. diastolic.

His appearance at this time is shown by the accompanying photograph (Fig. 1).

BLOOD ANALYSIS

		Mg. Per 100 C.c.
April 19, 1916.	Urea N.	12.3
	Creatinin	1.3
	Uric acid	6.15
	Glucose	102.0
April 24, 1916.	Nonprotein N.	68.2
	Uric acid	3.0
May 20, 1916.	Uric acid	7.18

URINALYSIS

April 18, 1916.	Light yellow, clear, slightly acid to litmus
	Sp. gr. 1.018
	Albumin ..... Slight trace
	Indican ..... Trace
	Glucose ..... Absent
	Few hyaline casts; few leukocytes and red blood cells

Subsequent Course.—April 18. Through the kindness of Dr. Alexander Lambert, to whom we wish to express our thanks, the patient was transferred to the metabolism ward of the Sage Institute. Previously he had been on the general medical service of Bellevue Hospital, Second Division.

April 19. First calorimeter observation.

April 24. Second calorimeter observation.

April 25. Transferred to the hospital of the Rockefeller Institute.

April 26. Roentgen therapy begun.

April 29. Following Roentgen-ray treatments on two successive days (25th and 26th), the patient did not feel well yesterday; headache, weakness, bowels constipated. Condition better today, however.

April 30. Transferred to metabolism ward of Bellevue Hospital.

May 1. Third calorimeter observation. Transferred to hospital of Rockefeller Institute.

May 10. With continued Roentgen-ray dosage the total white count has come down almost progressively. A few days previous to entrance it was 55,000. Two days ago it was 22,000. Patient has been symptom-free save for tenderness over the spleen at times.

May 18. Transferred to the metabolism ward in Bellevue Hospital.

May 19. Fourth calorimeter experiment. Transferred to hospital of the Rockefeller Institute.

May 20. Five days ago patient had severe nosebleed. Size of spleen remains stationary. At times patient has considerable pain in left flank with tenderness over spleen.

Since coming to hospital patient has noticed a small, non-tender mass in right groin, more prominent on straining. Examination shows a loose, right inguinal ring with impulse and visible bulge on cough.

Repeated Roentgen-ray exposure has caused tanning of the whole skin, with some erythema and desquamation over back and thighs.

June 10. Another slight nose-bleed yesterday. Patient is exercising a little each day; feels very weak, however.

Percussion dulness of heart less in both directions by 1 cm., and the murmur is loudest in fifth space, midclavicular line.

June 26. The spleen is growing in size and is much firmer, with a more prominent edge than on entrance. It has extended to the right 2 cm. The

liver edge is palpable 1.5 cm. below the costal margin. There are palpable almond-sized lymph nodes in the neck on either side, in axillae and groins.

There is erythema and desquamation of the skin over the left chest in the axillary line due to the Roentgen ray. There are several very tender areas over the spleen.

July 18. Admitted to St. Luke's Hospital for radium treatment. In applying radium the splenic region was divided into four equal parts and each part was subjected to a two-hour application of radium, making each period eight hours in all.

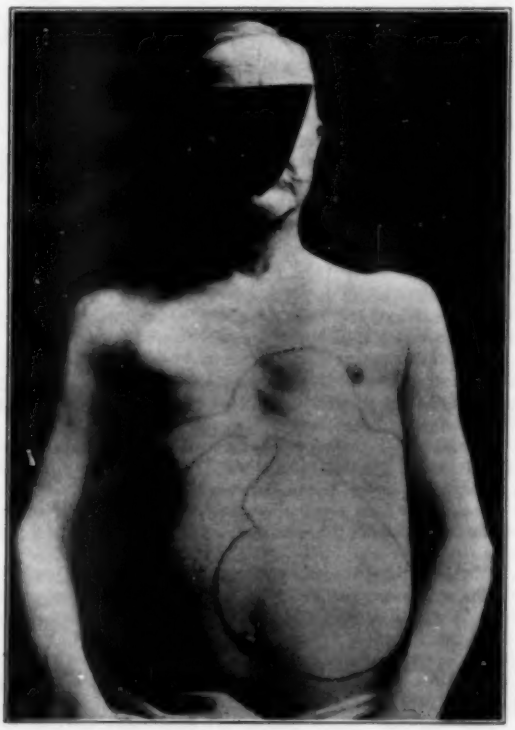


Fig. 1.—Anthony W., April, 1916, before treatment.

July 25. Radium applied.
August 10. Radium applied.
August 17. Radium applied.
August 26. Radium applied.
August 30. Discharged from hospital.
September 9. Radium applied.
September 23. Radium applied.

Oct. 24, 1916, entered metabolism ward at Bellevue Hospital. Since his first radium treatment the patient has had no pain and very little tenderness over the spleen. The spleen has grown smaller and he has felt much better.

He has had less dyspnea and can walk as far as one mile (slowly) without fatigue.

Physical Examination shows the heart enlarged to the left, with a soft, blowing systolic murmur at the apex, transmitted to the axilla and toward the sternum. The spleen is distinctly smaller than when he was first observed. His appearance at this time is shown in Figure 2.

October 25. Fifth calorimeter experiment.

Blood Analysis: Uric acid, 3.6 mg. per 100 c.c. of blood.

Fig. 2.—Anthony W., Oct. 25, 1916, after Roentgen and radium treatment.

DISCUSSION OF RESULTS

The basal metabolism in a case of chronic lymphatic leukemia showed a rise of 44 per cent. above the average figure for normal men of the patient's age. This finding is similar to those of Grafe, Magnus-Levy, Kraus and Bohland. The high metabolism in leukemia is especially interesting, because (in one case, at least) there was nothing about the general appearance to lead one to suppose that the metabolism was increased. In Graves' disease, as already pointed out

TABLE 2.—Leukemia. Data of—

Subject, Date, Weight. Surface Area. Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Anthony W. 4/19/16 75.9 Kg. 1.96 Sq. M.	Prelim.	12:00	.....	.....	.....	.....	.....	.....	.....
	1	1:00	38.0	34.3	0.76	57.6	0.311	113.6	115.4
	2	2:00	34.5	33.5	0.75	56.8	0.311	110.5	112.2
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Anthony W.* 4/24/16 75.4 Kg. 1.96 Sq. M.	Prelim.	12:02	.....	.....	.....	.....	.....	.....	.....
	1	1:02	33.4	34.3	0.71	48.0	0.402	.....	102.8
	2	2:02	33.4	32.6	0.75	55.3	0.402	.....	113.0
	Aver.	.....	.....	.....	.....	.....	.....	109.5	.....
Anthony W. 5/ 1/16 78.8 Kg. 1.97 Sq. M.	Prelim.	11:41	.....	.....	.....	.....	.....	.....	.....
	1	12:31	27.6	26.8	0.75	39.1	0.296	88.4	88.3
	2	1:41	40.1	36.2	9.80	61.5	0.415	121.1	128.5
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Anthony W. 5/19/16 75.1 Kg. 1.96 Sq. M.	Prelim.	10:39	.....	.....	.....	.....	.....	.....	.....
	1	11:39	32.2	30.7	0.79	50.0	0.442	101.9	104.1
	2	12:39	34.4	32.0	0.78	56.0	0.442	106.1	110.7
	Aver.	.....	.....	.....	.....	.....	.....	.....	.....
Anthony W. 10/25/16 77.8 Kg. 1.98 Sq. M.	Prelim.	11:55	.....	.....	.....	.....	.....	.....	.....
	1	12:56	30.4	26.1	0.85	46.0	0.592	.....	94.5
	2	1:55	31.3	31.0	0.74	59.2	0.592	.....	103.1
	Aver.	.....	.....	.....	.....	.....	.....	94.4	.....

TABLE 3.—Leukemia.—

Name and Date	Food				Food N., Gm.	Urine N., Gm.
	Total Calories	Calories per Kg.	Carbohydrate, Gm.	Fat, Gm.		
Anthony W. 4/19/16	1,860	25	144	110	11.0	10.2
4/20/16	2,534	33	212	138	14.9	10.3
4/21/16	2,450	32	215	122	12.7	11.8
4/22/16	2,611	34	214	144	15.2	10.4
4/23/16	2,524	33	196	142	15.5	10.9
4/24/16	2,276	..	175	128	14.2	12.0
5/ 1/16	2,037	..	160	113	12.9	10.2

* Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.

—Calorimeter Observations

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
.....	37.5	..	..	....	..	..	..	....	.....	Basal
110.5	37.4	73	60	0.76	..	..	..	....	.....	Restless
108.2	37.4	71	36	0.74	..	..	..	....	.....	Quiet
.....	.....	..	..	0.75	7	79	14	1.48	57.1	
.....	37.5	..	..	....	..	..	..	....	.....	Basal
104.2	37.5	60	32	0.70	..	..	..	....	.....	Quiet; work-adder very sensitive
110.6	37.5	62	33	0.74	..	..	..	....	.....	Quiet; work-adder very sensitive
.....	.....	..	..	0.72	10	86	4	1.45	55.9	
.....	37.3	..	..	....	..	..	..	....	.....	Basal
79.6	37.2	62	31	0.74	..	..	..	....	.....	50 min. period; very quiet
135.1	37.3	59	44	0.80	..	..	..	....	.....	70 min. period; fairly quiet
.....	.....	..	..	....	9	68	23	1.36	53.2	Per period
.....	37.2	66	..	....	..	..	..	....	.....	Basal
98.5	37.1	65	36	0.79	..	..	..	....	.....	Slightly restless
113.3	37.2	65	31	0.78	..	..	..	....	.....	Slightly restless
.....	.....	..	..	....	11	66	23	1.36	53.4	
.....	37.1	..	..	....	..	..	..	....	.....	Basal
93.3	37.1	53	32	....	..	..	..	....	.....	Fairly quiet (61 min. period)
100.7	37.1	55	38	....	..	..	..	....	.....	Restless; coughed (59 min. period)
.....	.....	..	..	0.78	17	62	21	1.21	47.7	

—Clinical Data

Excreta* N., Gm.	Nitrogen Balance, Gm.	Uric Acid, Gm.	Purin N., Gm.	Body Weight, Kg.	Urine Volume, C.c.	Blood Pressure, Syst.-Diast.
11.3	—0.3	.....	.....	75.9	1,140	168-95
11.8	+3.1	0.522	0.014	76.2	1,220	
12.2	+0.5	0.520	0.017	76.1	1,300	
11.9	+3.3	0.480	0.006	75.1	1,300	
12.5	+3.0	0.500	0.005	76.5	1,310	
12.4	+0.8	0.563	0.008	75.4	1,350	140-98
11.5	+1.4	0.509	0.016	76.8	1,666	

in the Fourteenth Paper of this series, there are a number of manifestations—the profuse sweating, the hot, flushed skin, the tachycardia, etc.—which are probably due to the high metabolism. Practically all such signs were lacking in this leukemic. His skin was not hot or flushed; he had no tachycardia; he may possibly have had a tendency to sweat rather more easily than a normal individual. Moreover, there was no nervous element. He was perfectly placid, was rather interested in the experiments, was not in the least worried by being placed in the calorimeter, and was fairly quiet in all the observations. Nevertheless, he had a very high metabolism. The results of the calorimeter experiments are collected in Table 2.

This increased metabolism was apparently not due to increased combustion of body protein, for the patient was in nitrogen equilibrium on a nitrogenous intake of 13 to 15 gm. per day, and, moreover, he was maintaining his weight on an intake of 2,400 calories. The figures for food and urine analysis are given in Table 3.

An inspection of the respiratory quotients shows them to be rather lower than those of normal individuals who have fasted sixteen hours, but no lower than those of many patients with Graves' disease[39] with a similar increase in metabolism. These low quotients are probably due, as in Graves' disease, to the more rapid consumption of the glycogen store because of the high metabolism.

As to what causes the increased metabolism in leukemia we can not venture an opinion. Grafe thought it was the result of the very active metabolism of young white cells. His experiments on the metabolism of blood do show an increased oxygen consumption in leukemic blood, but he could account for only about 10 per cent. of the total oxygen consumption as being due to leukocytes. Just how he could explain a rise of 40 or 60 per cent. in the basal metabolism on that ground, we do not quite understand.

Grafe's supposition that the high metabolism resulted from the leukocytes, led us to plot the heat production and leukocyte counts of our patient and then, from the literature given in Table 1, to see whether there was any relation between the leukocyte count and the level of the metabolism. Among different cases there was no such relation, but in individual cases there was evidence of a certain parallelism. As the leukocyte count fell, the metabolism did likewise, and vice versa. But the fall in leukocytes is always very much greater than that in the metabolism. This statement applies to Grafe's cases T. S. and C. L., and also possibly to a slight extent to our case, as may be seen by consulting Figure 3. Of course, the lack of relationship between metabolism increase and leukocyte count in different cases

39. Du Bois, E. F.: Metabolism in Exophthalmic Goiter, THE ARCHIVES INT. MED., 1916, **17**, 915.

does not in the least disprove Grafe's theory, for it is rather the rate of production of white cells and not their total number that is the determining factor. Further work on the metabolism of leukocytes could be done to advantage.

Let us now consider what effect the Roentgen rays had on the metabolism. Unfortunately, in this connection we have observations on the basal metabolism only. The data on the nitrogen metabolism

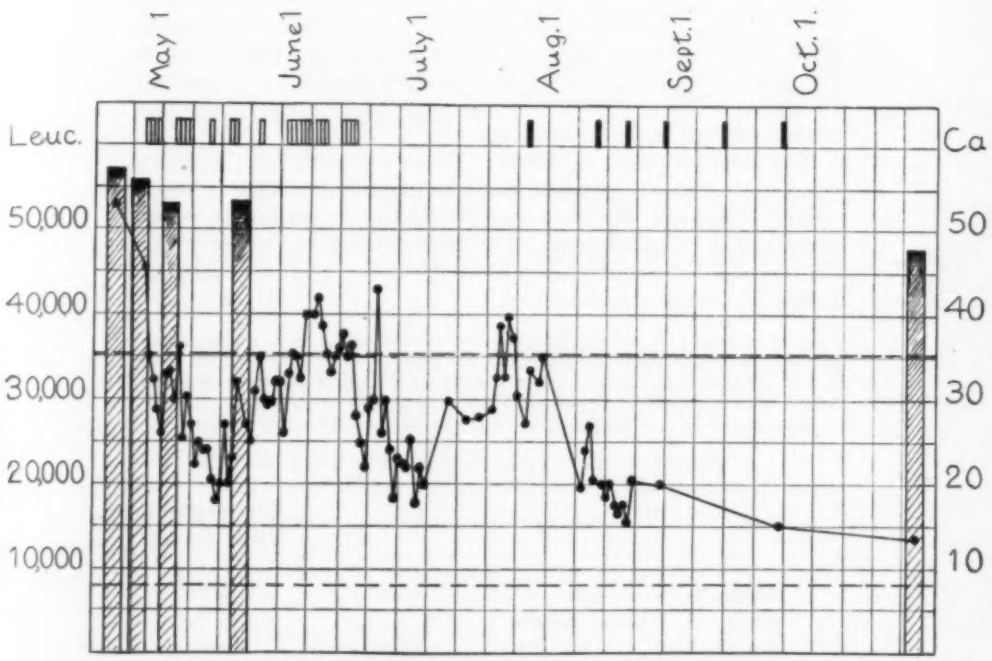


Fig. 3.—Chart showing the basal metabolism, shaded columns, and the leukocyte count, black dots and lines. The hollow rectangles at the top indicate Roentgen treatments, and the black ones radium treatments. The perpendicular rulings indicate periods of one week. The upper broken line represents the average basal metabolism for men from 50 to 60 years of age; the lower, the normal leukocyte count.

were obtained only while the patient was in the Sage metabolism ward, so that all the figures given in Table 3 were obtained before the irradiation was begun.

In Figure 3 the leukocyte count and the basal metabolism are compared. It will be seen that both of these were falling before the irradiation was begun. A slight fall in the basal metabolism occurred five days after the beginning of irradiation but was no greater than

had previously occurred spontaneously, and after twenty-three days, during which ten treatments were given, it had shown no further decrease. The Roentgen ray had no appreciable effect on the basal metabolism in this case. From the appearance of the leukocyte curve it looks as though a drop had been caused in the first few days. Prolonged treatment, moreover, entirely failed to produce an aleukemic blood picture.

The effect of the radium treatment at St. Luke's Hospital is rather more striking. The leukocyte curve shows a much more consistent fall after the radium exposures than after the Roentgen therapy. With this drop in the leukocytes the basal metabolism fell to 47.7 calories per square meter per hour, which is 36 per cent. above the normal average for men of the patient's age.

The results obtained on Anthony W. have recently been confirmed by a patient with myelogenous leukemia studied in the Massachusetts General Hospital in the service of Dr. Edsall. A preliminary report of the findings is given below. The basal metabolism was determined with the small Benedict Universal Respiration Apparatus, using the method of indirect calorimetry.

Dr. J. G., aged 51, height 171 cm. Six months previous to examination it was noticed that the patient's color was not good. For the previous six weeks he had suffered from weakness and lassitude. His blood picture was that of myelogenous leukemia and the spleen was enormously enlarged.

November 9 he felt much better. The size of the spleen was unchanged.

TABLE 4.—CLINICAL DATA IN CASE OF DR. J. G.

Date	Weight, Kg.	Leukocytes	Basal Metabolism Cals. per Sq. M. per Hr. (Linear Formula)
10/12/16	83.0	296,000	65.3
10/16/16	Radium treatment		
10/17/16	83.0	240,000	60.7
11/ 9/16	81.5	73,000	51.0

DIRECT AND INDIRECT CALORIMETRY

The agreement between the two independent methods of direct and indirect calorimetry in the case of Anthony W. is unusually close. The figure for total calories as measured by the former method is 1,054.0; by the latter method, 1,049.4. This indicates that there is no profound and unsuspected abnormality in the intermediary metabolism.

The water elimination was unusually high, 53 gm. an hour. He lost on an average of 29.5 per cent. of his calories in the vaporization of water under the atmospheric conditions in which normal men lose only 24.1 per cent. in this manner.

SUMMARY AND CONCLUSIONS

A man with chronic lymphatic leukemia was studied five times in the respiration calorimeter. When first observed his metabolism was 44 per cent. above the average normal, falling a little with rest in bed. Intensive treatment with Roentgen rays caused a drop in the leukocyte count but did not appreciably affect the level of his metabolism. The water elimination through skin and respiratory passages was unusually high. Direct and indirect calorimetry gave total results which were almost identical, and no abnormal respiratory quotients were found.

After treatment with radium, a further and very marked fall occurred in the leukocyte count and, at the same time, a slight fall occurred in the basal metabolism.[40]

477 First Avenue.

40. The writers wish to thank Dr. Alexander Lambert for his courtesy in transferring the patient to the metabolism ward; Dr. Montgomery and Dr. Witherbee of the Rockefeller Hospital for the data of Roentgen-ray treatments; and Dr. Karl M. Vogel of St. Luke's Hospital for the data of radium treatments.

CLINICAL CALORIMETRY

TWENTY-FOURTH PAPER

METABOLISM IN THREE UNUSUAL CASES OF DIABETES*

F. C. GEPHART, PH.D., J. C. AUB, M.D.,
E. F. DU BOIS, M.D., AND GRAHAM LUSK, Sc.D.
WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM
NEW YORK

The treatment of diabetes by the method of prolonged fasting has been conspicuously successful in recent years. The present paper deals with the measurement of the respiratory exchange and the total heat production of three patients, and supplements Paper 17 of this series by Allen and Du Bois,[1] which contains a review of the literature.

The patients were:

1. A diabetic woman who had been fasted to a state of emaciation, and who had a low tolerance for carbohydrate.

2. A diabetic man who had had the disease in a mild form, who showed a tolerance for 40 gm. of carbohydrate, but who was made completely diabetic (D:N = 3.84) on the second day after the administration of a diet containing considerable quantities of protein and fat. Subsequently, virtual starvation led within sixty hours to the disappearance of the sugar from the urine.

3. A diabetic man who at first manifested resistance to the influence of fasting, whose metabolism indicated complete diabetes, in that he had a D:N ratio of 3.97 when given meat and fat, and also eliminated that quantity of beta-oxybutyric acid theoretically derivable from the fat metabolism of the time. This patient subsequently developed a tolerance for 250 gm. of carbohydrate.

METHODS

The methods and calculations used in these observations were the same as those in the cases previously reported from this laboratory by Allen and Du Bois. The respiratory quotients and total metabolism were determined by the method described in the previous papers on

* Submitted for publication Feb. 14, 1917.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

1. Allen, F. M., and Du Bois, E. F.: Metabolism and Treatment in Diabetes, THE ARCHIVES INT. MED., 1916, **17**, 1010.

clinical calorimetry,[2] and, unless otherwise stated, were all basal observations; that is, they were made at least fifteen to eighteen hours after the last ingestion of food. Good alcohol check observations, made just before and after the observations on Cyril K., and at about the same time as the studies of the other two cases reported, assured the accuracy of the findings. The calculations involved in the determination of the protein respiratory quotient, complicated by glucose excretion from protein, were thoroughly discussed in Paper 17 of this series.[3]

Urine: The urinary examinations were made for total nitrogen by the Kjeldahl method; for ammonia, by the Folin method; for urinary sugar, by the Benedict method; for acetone bodies, by Shaffer's method; beta-oxybutyric acid, by Shaffer's method; sodium chlorid, by the Volhardt method.

Blood: Blood sugar was determined by the method of Lewis and Benedict; nonprotein nitrogen, by Bock and Benedict's modification of Folin's method; urea, by the method of Van Slyke and Cullen; blood fat, by Bloor's method. The carbon dioxid combining power of the plasma was determined by the method of Van Slyke; alveolar air determinations were made by the Plesch-Higgins method.

The dextrose to nitrogen ratios are calculated as follows: The carbohydrate value in the food ingested is subtracted from the total glucose found in the urine. The remaining glucose excretion, divided by the total nitrogen excreted during the same period, gives the dextrose to nitrogen value. Its usual maximum value, as first shown by Mandel and Lusk,[4] is 3.65.

ROUTINE

The two male patients were kept in the Sage metabolism ward at Bellevue Hospital under the routine observation described in Paper 3 of this series.[5]

The one female patient was left in the open ward for one day under constant observation of the metabolism nurses. Every attempt was

2. Riche, J. A., and Soderstrom, G. F.: Clinical Calorimetry, Papers 2, 3 and 4, The Respiration Calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital; Gephart, F. C., and Du Bois, E. F.: The Organization of a Small Metabolism Ward; The Determination of the Basal Metabolism of Normal Men and the Effect of Food, THE ARCHIVES INT. MED., 1915, **15,** 805-867.

3. Allen, F. M., and Du Bois, E. F.: Loc. cit., Note 1, p. 1018.

4. Mandel, A. R., and Lusk, G.: Stoffwechselbeobachtungen an einem Falle von Diabetes mellitus, mit besonderer Berücksichtigung der Prognose, Deutsch. Arch. f. klin. Med., 1904, **81,** 472.

5. Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 3, The Organization of a Small Metabolism Ward, THE ARCHIVES INT. MED., 1915, **15,** 829.

made to have all diets administered as accurately as possible, and composed of simple foodstuffs of known composition. The careful collection of urinary samples, by separate bottles for each voiding, has been described.

REPORT OF CASES

CASE 1.—*History.*—Anna H., aged 31, married, born in United States. Occupation, telephone operator. Weight 32.5 kg.; height 169 cm.

The patient was transferred for one day to Bellevue from the Rockefeller Hospital, where she had been under the care of Dr. Fitz.

Family history and physical history were not remarkable.

She was married three and a half years prior to admission; she had had two miscarriages; health was good until June, 1915. She weighed at that time 145 pounds (66 kg.) with her clothes; then marked polydipsia and polyuria developed, with loss of weight and strength. July 4, 1915, sugar was found in her urine. August 5, a fast of three days made her sugar-free but in September she again had glycosuria.

October 16 she entered the Rockefeller Hospital and remained there five months. She weighed on entrance 49 kg. After fasting six days she became sugar-free, but in order to keep her so she was given a very low diet. For the two months previous to this observation her average total intake was 570 calories a day, made up of whisky (70 to 150 c.c.) and an average of 26 gm. of protein, 17 gm. of fat, and no carbohydrate. This food was taken mostly in the form of eggs. The day previous to the calorimeter determination she received whisky, 30 c.c.; protein, 30.9 gm.; fat, 23.4 gm.; carbohydrate, 2.5 gm., containing in all 458 calories.

The physical examination was negative save for extreme emaciation. Knee jerks were not obtained.

She went into the calorimeter March 31, 1916. During the next few months her tolerance remained low, she lost weight steadily and died July 18, 1916. Permission for necropsy was refused.

Summary.—A case of diabetes of nine months' duration in a young woman. Her sugar tolerance is very low. She can take two to six eggs a day and 100 c.c. of whiskey and remain sugar-free, but if more food is given, sugar appears in the urine. For five months she has been on a very low calory diet at the Rockefeller Hospital (see the foregoing) and her urine has been free from sugar.

I. Her total metabolism is the lowest recorded in the literature, being only 23.2 calories per square meter per hour, which is 37 per cent. below the average basal normal in women. Since her original weight with clothes had been 66 kg., one may be permitted to assume a weight of 62 kg. without clothes. Had her metabolism been normal for this weight, it would have been 63.3 calories per hour instead of 29.4 calories, which were actually measured when her weight had fallen to 32.5 kg. The extreme emaciation which had resulted in a reduction of body weight to nearly half of what it was originally, reduced the metabolism so low that only 40 per cent. of the original heat production was necessary for life. This reduction in metabolism is one of the theoretical benefits of the Allen fasting treatment.

II. The nitrogen excretion in the urine (0.39 gm. per hour) is the quantity commonly found in normal people. The total metabolism, however, is so low that the percentage of calories from protein is quite high, 35 per cent. (15 per cent. being the average normal).

III. The respiratory quotients average 0.82, a normal figure. From this, one may calculate that fat gives 39 per cent. of the calories of metabolism and carbohydrate 26 per cent. This corresponds to the utilization of 44 gm. of carbohydrate daily, and, since none was given in the food, these results are difficult to interpret.

CASE 2 (Table 1).—*History.*—The case of Joseph D. is unusual because of the sudden change from a rather mild diabetes to one of the greatest severity, followed by rapid recovery of sugar tolerance.

Joseph D., aged 33, single, born in Russia. Occupation, carpenter. Admitted to Bellevue Hospital Nov. 9, 1915; discharged Nov. 29, 1915.

The patient was always well until six years prior to admission, when he had a chancre. He took four to five glasses of beer a day and sometimes smoked thirty or forty cigarets a day. His weight three years prior to admission was 89.1 kg.; now it is 56.8 kg.

Three years prior to admission, without known cause, he became very thirsty, hungry and weak. Two years previously sugar was found in the urine. He was given a diet with carbohydrate much reduced in quantity, and also sodium bicarbonate. His urine remained free from sugar for over a year, when he gave up dieting and glycosuria recurred. Then his former symptoms returned; his eyesight had been rapidly failing, so that he had difficulty in reading. For the previous three months he had been at Gouverneur, Bellevue and City Hospitals. He felt well save for weakness and hunger.

Physical Examination.—Emaciated, poorly developed, hollow chested man; face flushed and slightly cyanotic; breath smelled of acetone; tongue deep red and papillae prominent; throat and tonsils deep red and glazed. There was marked clubbing of fingers.

Lungs: Percussion showed dulness at both apices, particularly behind, with narrowing of both apical isthmuses; the breath sounds here were rather sharp and high pitched; voice sounds slightly nasal and tactile fremitus diminished; no râles heard.

Reflexes: Neither knee jerks nor ankle jerks could be obtained.

Extremities: From the knee down there was dulling of sensation for touch, poor differentiation of sharp and dull pressure, and of heat and cold. This was most marked on the inner side of the lower legs.

Wassermann reaction positive.

Blood pressure: systolic, 90 mm.; diastolic, 75 mm.

When transferred to Bellevue Hospital the patient was placed in the metabolism ward. Here his diet was changed from a very liberal allowance to one containing only 1,500 calories, with 40 to 50 gm. of carbohydrate and 15 gm. of nitrogen. With this intake his sugar excretion fell in five days from 72 gm. a day to 22 gm., and the morning urine of the sixth day (November 15) was free from sugar. This led us to believe that the case was comparatively mild, and our opinion was checked by a calorimeter observation. The respiratory quotient was 0.79, a normal value, indicating carbohydrate oxidation.

The patient complained bitterly of low calorie diets, so it was decided to give large quantities of meat and fat. After the calorimeter observation on November 15 he was therefore given a diet containing 3,000 calories, with 25 gm. of protein nitrogen and only 3 gm. of carbohydrate. The diet pleased the patient, but in the following fifteen hours, with 3 gm. carbohydrate in the food, he excreted 25.8 gm. of glucose and 14.9 gm. of nitrogen. The D:N ratio

TABLE 1.—Showing Sudden Change—

Name and Date	Temperature		Food			Food N., Gm.	Urine N., Gm.	Excreta N.,[1] Gm.	Nitrogen Balance, Gm.
	Max.	Min.	Total Calories	Carbohyd., Gm.	Fat, Gm.				
Joseph D. 11/10/16	99.2	98.8	1,521	48	104	14.0	14.6	16.0	−2.0
11/11/16	98.6	97.8	1,495	42	102	14.6	16.8	18.3	−3.7
11/12/16	98.8	97.0	1,576	41	102	15.0	17.8	19.3	−4.3
11/13/16	98.8	97.6	1,724	41	104	14.8	16.8	18.3	−3.5
11/14/16	98.4	98.0	1,580	37	97	13.3	15.9	17.2	−3.9
11/15/16	98.8	98.0	3,007	3	261	24.6	17.9	20.4	+4.4
11/16/16	99.6	98.4	3,135	3	280	25.2	22.8	25.3	−0.1
11/17/16	100.4	98.8	1,849	2	138	12.7	12.3[3]	13.6	−0.8
11/18/16	99.8	99.6	558	?	7	0.5	10.0[4]	10.1	−9.6
11/19/16	98.8	98.0	567	3[2]	17	4.8	9.6[5]	10.1	−5.3
11/20/16	98.8	98.8	674	2	17	3.7	8.5[6]	8.9	−5.2
11/21/16	98.0	97.8	1,091	2	57	4.5	11.2	11.7	−7.1
11/22/16	98.2	97.0	1,318	2	76	6.3	11.9	12.5	−6.2
11/23/16	97.0	97.0	1,527	25	85	7.8	11.5[7]	12.3	−4.5
11/24/16	98.0	97.8	1,615	28	88	9.5	12.1[8]	13.1	−3.6
11/25/16	99.2	97.4	2,120	50	132	12.6	12.2[9]	13.6	−1.0
11/26/16	99.2	98.4	2,059	70	122	12.5	10.6[10]	11.9	+0.7
11/27/16	99.0	98.0	733	22	27	3.9	6.9[11]	7.3	−3.3
11/28/16	98.8	98.0	2,005	56	124	12.3	8.8	10.0	+2.3

1. Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.
2. Bread crumbs found in bed.
3. 16 hours 55 minutes.
4. 29 hours 35 minutes.
5. 25 hours.
6. 24 hours 30 minutes.

was 1.53. The next day, November 16, the patient felt very well and was allowed to sit in a chair. The diet was continued. The urine of this day showed 90.6 gm. of glucose and a complete D:N ratio, 3.84.

November 17 the diet was reduced to 1,850 calories containing 12.7 gm. of nitrogen and but 2 gm. of carbohydrate. Even with this diet the patient excreted 40.4 gm. of glucose and had a D:N ratio of 3.09. During the day the patient had abdominal pain and marked diarrhea, with mucus and some blood. Toward evening he complained of pain in the left jaw. Six hours after his last meal, which contained 65 gm. of fat and 7 gm. of protein nitrogen, a calorimeter observation was made and the respiratory quotient was found to be 0.714. This value is low, and the calculations show that he was oxidizing almost no carbohydrate. The D:N ratio of 2.53 confirmed the low respiratory quotient.

November 18 the patient was given a very low diet, only 550 calories, mostly in the form of alcohol, with less than 1 gm. of carbohydrate or protein. However, he managed to steal a slice of bread, so that an accurate D:N ratio for the day cannot be given. If one approximately estimates the weight of a slice of bread to be 40 gm., however, the D:N ratio would have been about 2.

A large alveolar abscess was discovered and opened and 2 or 3 c.c. of pus pressed out. The diarrhea stopped and the patient felt well and hungry.

—FROM MILD TO SEVERE DIABETES

Body Weight, Kg.	Urine Volume, C.c.	Calories per Kg.	Blood Pressure, Syst. Diast.	Urine Glucose, Gm.	NH_3N, Gm.	Alcohol, Cals.	Sodium Bicarb., Gm.	D : N Ratio	Acetone plus Diacetic Acid
45.7	1,420	33	.....	71.97	1.295	...	20		
46.3	1,940	33	.....	45.09	0.556	...	20		
46.3	2,040	34	.....	37.45	0.628	80	15		
46.9	3,220	37	.....	32.90	0.584	214	15	....	0.65
47.1	3,420	34	.....	22.20	0.579	187	20	0	0.42
46.0	4,040	..	90-75	25.80	0.707	...	15	1.27	1.77
45.5	3,900	69	95-75	90.57	3.143	...	20	3.84	2.44
44.4	1,302	42	.....	40.38[2]	2.220[2]	281	30	3.09	2.02
44.0	1,000	13	95-75	41.33[4]	1.130[4]	482	25	2.0 (?)	0.58
45.6	3,880	12	.....	2.74[5]	0.585[5]	...	20	1.17[12]	
44.7	3,760	17	95-75	0.00[6]	0.264[6]	441	30		
....	3,880	..	.....	0.00	0.304	441	18		
44.5	3,340	29	.....	0.00	.....	441	10		
44.4	3,400	34	100-80	0.00	.....	441	12		
....	3,020	..	.....	0.00	.....	402			
42.9	3,180	46	.....	0.00	.....	361			
44.7	3,000	42	.....	Trace	.....	321			
....	4,400	..	.....	Sl. trace	.....	321			
....	2,840	..	.....	0.00	.....	401			

7. 25 hours.
8. 23 hours 20 minutes.
9. 23 hours 40 minutes.
10. 24 hours 55 minutes.
11. 23 hours 5 minutes.
12. Eight-hour specimen.

November 19, the respiratory quotient was again nearly normal, 0.775, and by noon the urine was free from sugar.

November 23, the patient was put on a mixed diet with daily increasing carbohydrates.

November 26, with 70 gm. of carbohydrate in the food, there was a faint trace of glucose in the urine.

November 27, low diet day.

November 28, mixed diet containing 50 gm. of carbohydrate. The patient was returned to the hospital from which he had come.

It was difficult to keep this patient on a restricted diet except under constant supervision. This could be managed in the metabolism ward, but not in the open ward.

On further treatment he did not improve, and Jan. 4, 1916, he died in diabetic coma.

Summary.—This case shows very clearly how rapid may be the change in tolerance for carbohydrate in diabetes. The urine of the patient had become free from sugar when given a mixed diet con-

taining 40 gm. of carbohydrate, but the diet high in meat and fat, and alveolar abscess with the diarrhea, were sufficient to make him a complete diabetic; that is, with the theoretical D:N ratio continuing for one day. This is shown in Table 2.

TABLE 2.—Illustrating Rapid Change in Carbohydrate Tolerance

Joseph D., a diabetic whose urine was free from sugar, became completely diabetic (D:N = 3.84) sixteen hours after the ingestion of meat and fat in large quantity, and, on reducing the diet, became free from sugar in about sixty hours.

Date	Day	Diet	Nitrogen in Urine per Hour	D:N	R. Q.	Calories per Sq. M. per Hour	Variation from Normal in Per Cent.
1915							
11/15	1	Basal, then high protein...	0.385	....	0.79	37.9	— 5
11/16	2	High protein.....	.....	3.84			
11/17	3	Less protein.....	0.356	2.53	0.714	50.7*	+28*
11/18	4	Fasting and stolen bread					
11/19	5	Fasting and stolen bread..	0.330	0.0	0.78	38.6	— 2

* Restless during both hours while in the calorimeter. Had pain during the last hour and asked to be taken out.

Accompanying this absolute inability to metabolize glucose, there developed at the same time some inability to metabolize fat to its normal end-products. Unfortunately, the only figures we have to report are the values of urinary ammonia and of acetone and diacetic acid excretion. The ammonia values suggest that the formation of acetone bodies was only in moderate quantity.

When the complicating factors were eliminated, the patient rapidly improved and again tolerated a mixed diet of 2,000 calories, containing 50 gm. of carbohydrate.

While the D:N ratio may be altered by the ingestion of carbohydrate food, the respiratory quotient quickly reveals if carbohydrate is being metabolized. The validity of the urinary D:N = 2.53 on November 17 is checked excellently by the calorimeter observations of the same date which showed a very marked drop in the respiratory quotient to 0.714, indicating that very little glucose was being oxidized. Hence, on this day no carbohydrate could have been surreptitiously taken by the patient.

The patient was restless while in the calorimeter on the day of diabetes, so that the increase of 28 per cent. in his metabolism is not to be accepted without qualification. The hourly urinary nitrogen was the same during all three calorimeter periods. It is possible that the

effect of the stimulus due to the high protein metabolism of Day 2 outlasted the presence of the stimulus itself.[6]

CASE 3[7] (Tables 3, 4 and 5).—*History.*—Cyril K., aged 19, single, college student, born in the United States.

The patient was admitted to the Presbyterian Hospital Dec. 7, 1915; transferred to Bellevue Hospital Dec. 14, 1915; retransferred to Presbyterian Hospital Dec. 23, 1915; discharged March 7, 1916.

The family history was negative. The patient's health was always good. Fourteen months prior to admission he passed a life insurance examination. There had been no recent infection. October 19 he weighed 78.2 kg. with his clothes on and was then feeling perfectly well. Early in November he began to lose weight, felt weak, tired, without ambition. November 15 a physician found 4.5 per cent. sugar in the urine. He was given a diet containing much meat, whole wheat bread and buttermilk. He had polydipsia and polyuria. About November 20 he weighed 70.5 kg. with his overcoat on. December 1 he felt drowsy and slept a great deal. December 4 he felt very weak, nauseated and vomited, the drowsiness continuing. His last food was December 6 at 7 p. m.

December 7 he entered Presbyterian Hospital. Hemoglobin, 80 per cent.; white cells, 15,500; Wassermann negative.

Under Dr. Geyelin's care he was fasted until December 11. He seemed to be getting more drowsy; respirations were of the air hunger type; he was nauseated. Each day he received 53 to 114 gm. soda bicarbonate, most of it intravenously.

December 11 he was given food, as fasting did not seem to improve his condition. He received mostly milk and eggs. December 13 his condition improved. He was less drowsy and there was less air hunger.

December 14, transferred to Bellevue Hospital.

Physical Examination.—The patient was 6 feet 2 inches tall; of large frame; very thin, but not yet emaciated, with flushed face, pinched nose, drooping eyelids. He was slightly drowsy, but mentally clear. There was a marked acetone odor to the breath. Respirations were deep, 18 to the minute. The mucous membrane, gums and tongue were bright red and glazed. There were small furuncles on the right pinna and two on the left side of the neck. The remainder of the physical examination was not remarkable.

December 15. Put in the calorimeter this morning after a milk diet.

December 16. The patient read the newspaper; no nausea, said he felt very much better than two days previously. Clinically, he was much improved, although the laboratory findings did not indicate much change. He was placed in the calorimeter after a day of protein food.

December 18. Basal calorimeter observation this morning. Abscess on back of neck incised and 2 c.c. of greenish pus evacuated. Started fasting.

December 19. Abscess dressed; 2 c.c. pus obtained. Blood examination showed: white cells, 10,200; red cells, 5,746,000.

December 20. Basal calorimeter observation.

December 21. Still fasting; patient improving steadily; breathing normal; tongue clean; patient not at all drowsy, but reading all day; abscess still discharging small amount of pus.

---

6. Lusk, G.: Animal Calorimetry, Paper 11. An Investigation Into the Causes of the Specific Dynamic Action of the Foodstuffs, Jour. Biol. Chem., 1915, **20,** 569.

7. A preliminary report of this case has been given by Geyelin and Du Bois: A Case of Diabetes of Maximum Severity with Marked Improvement, Jour. Am. Med. Assn., 1916, **66,** 1532. Further details of the clinical and laboratory data will be published shortly by Geyelin.

TABLE 3.—Clinical Data in—

Name and Date	Body Weight, Kg.	Total Calories	Calories per Kg.	Food		Food N, Gm.	Fluid Intake, C.c.	NaCl Intake, Gm.	Sodium Bicarb., Gm.	Chalk, Gm.	Temperature	
				Carbohyd., Gm.	Fat, Gm.						Max.	Min.
Cyril K. 12/14/15	....	906	..	53.0	51.0	9.3	3,450	8.00+	25	15	Normal	
12/15/15	56.7	904	12	24.0	41.0	19.0	5,850	18.00	50	20	Normal	
12/16/15	56.3	456	9	0.4	5.6	16.2	4,525	19.98	55	20	Normal	
12/17/15	58.0	191	3	0.4	2.9	6.3	6,500	27.20	60	20	100.8	96.6
12/18/15	56.5	0	0	Fast	day	....	4,250	10.00	45	20	98.4	97.6
12/19/15	57.2	0	0	Fast	day	1.3	5,550	7.10	35	25	Normal	
12/20/15	56.9	60	1	6.0	0.3	2.6	3,850	8.00	30	20	Normal	
12/21/15	56.6	83	1	6.6	0.3	3.2	4,150	12.12	5	5	Normal	
12/22/15	54.3	108	2	11.4	0.4	3.4	4,050	17.19	..	..	98.2	97.4
12/23/15	....	...	..	....	....	....	.....	.....	..	..	.....	
2/15/16	....	...	..	252.0	6.0	9.5	.....	.....	..	..	.....	
2/16/16	....	...	..	270.0	10.9	7.0	.....	.....	..	..	.....	

* Excreta nitrogen calculated as urine nitrogen plus 10 per cent. of food nitrogen.
† Thirteen hours and forty-five minutes.
‡ Nonprotein nitrogen, 24.7 mg.; blood urea, 9.1 mg.; blood fat, 0.49 per cent.

TABLE 4.—

Subject	Age	Date	Height, Cm.	Weight, Kg.	Surface Area, Linear	Total Calories per Hour	Calories per Sq. M. per Hour
Case 3 (Cyril K.)....	19	12/15/15	187	56.7	1.79	81.9	45.7
		12/16/15	...	56.3	1.79	76.4	42.6
		12/18/15	...	56.5	1.79	72.2	40.3
		12/20/15	...	56.9	1.79	66.3	37.0
		12/22/15	...	54.3	1.75	62.8	35.9
		2/15/16	...	45.3	1.66	42.0	25.9
		2/ 8/16	180	48.2	1.72	50.0	29.1
Case 2 (Joseph D.)	33	11/15/15	170	45.5	1.48	56.1	37.9
		11/17/15	...	44.4	1.47	74.5	50.7
		11/19/15	...	45.0	1.48	57.1	38.6
Case 1 (Anna H.)....	31	3/31/16	160	32.5	1.27	29.5	23.2

* D:N during calorimeter period.

—A CASE OF DIABETES

Blood Pressure Syst. Diast.	Urine Vol., C.c.	Urine* N., Gm.	Nitrogen Balance, Gm.	Urine Glucose, Gm.	D:N Ratio	Urine NaCl, Gm.	NH_3 N., Gm.	Acetone + Diacetic Acid Gm.	Beta-oxy-butyric, Gm.	Alveolar CO_2 Tension, Mm. Hg	Blood CO_2 Vol. %	Blood Glucose, Mg.
.....	4,715	37.7	—28.9	118.5	....	.....	5.41	3.78†	55.2	....	....	.....
118-78	5,290	36.4	—19.3	167.9	3.97	13.21	5.214	5.61	70.9	....	29.2	.....
114-64	5,710	38.3	—23.7	153.4	4.01	16.37	3.537	4.99	75.1	{21.0 {15.1	28.4	.....
114-72	6,900	36.2	—30.6	140.2	3.87	22.85	3.818	.....	87.4	22.4	51.3	.....
108-60	3,080	20.0	—20.1	55.1	2.76	10.82	2.914	.....	56.5	22.9	52.0	0.150
102-70	4,700	16.7	—15.5	44.2	2.65	15.42	2.290	.....	56.8	30.6	73.9	.....
.....	4,080	14.1	—11.8	35.2	2.44	12.44	1.603	.....	41.2	33.7	75.8	0.177
104-64	6,000	14.4	—11.5	39.7	2.65	19.86	1.324	.....	26.2	....	....	0.170‡
104-70	3,770	13.3	—15.2	26.0	1.12	12.21	1.429	.....	11.0	{35.2 {31.0	78.2	0.151
.....	.....	....	.....	.....	....	.....	.....	.....	.....	....	72.1	0.206
.....	.....	....	.....	0.0								
.....	.....	....	.....	Trace								

—SUMMARY CHART—DIABETES

Variation from Average Normal, Per Cent.	R. Q.	Nonprotein R. Q.	D : N Ratio*	Per Cent. Calories from			Remarks
				Protein	Fat	Carbohyd.	
+15	0.687	0.699	5.05	21	79	0	After breakfast
+ 7	0.714	0.742	3.65	25	75	0	After breakfast
+ 2	0.707	0.706	2.63	21	79	0	Basal
— 7	0.721	0.718	2.21	15	82	2 (?)	Basal
—10	0.734	0.728	1.53	20	74	6	Basal
—25.	0.915	0.970	0.0	31	7	62	Basal
—27	0.860	0.872	0.0	16	37	47	Basal
— 5	0.790	0.787	0.0	17	60	23	Basal
+28	0.714	0.711	2.53	8	90	2 (?)	After dinner
— 2	0.775	0.769	0.0	16	66	18	Basal
—27	0.815	0.822	0.0	35	39	26	Basal

TABLE 5.—DATA OF CALORIMETER—

Subject, Date, Weight. Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Case 2 (Joseph D.)	Prelim.	11:39 a.m.	....	.....	.....	.....	.....	.....	.....
11/15/15									
45.5 Kg.	1	12:39	18.2	17.3	0.768	28.7	0.385	56.8	53.4
1.48 Sq. M.	2	1:39	18.6	16.7	0.812	27.8	0.385	55.4	58.0
Joseph D.	Prelim.	6:04 p.m.	....	.....	.....	.....	.....	.....	.....
11/17/16									
44.4 Kg.	1	7:04	22.6	22.5	0.730	24.1	0.356	73.6	68.1
1.47 Sq. M.	2	7:56	19.3	20.1	0.698	23.7	0.356	65.4	59.8
	Aver.	.....	....	.....	.....	.....	.....	.....	.....
Joseph D.	Prelim.	11:43	....	.....	.....	.....	.....	.....	.....
11/19/15									
45.6 Kg.	1	12:43	18.9	17.6	0.780	34.5	0.330	58.2	64.7
1.48 Sq. M.	2	1:43	18.0	17.0	0.770	34.1	0.330	56.1	60.2
	Aver.	.....	....	.....	.....	.....	.....	.....	.....
Case 2 (Cyril K.)..	Prelim.	12:31	....	.....	.....	.....	.....	.....	.....
12/15/15									
56.7 Kg.	1	1:31	23.3	23.6	0.718	31.1	1.34	.....	80.1
1.79 Sq. M.	2	2:31	25.1	27.3	0.656	36.4	1.34	.....	89.5
	Aver.	.....	....	.....	.....	.....	.....	81.9*	.....
Cyril K.	Prelim.	12:31	....	.....	.....	.....	.....	.....	.....
12/16/15									
5.66 Kg.	1	1:31	24.1	24.5	0.715	32.1	1.44	77.8†	93.6
1.79 Sq. M.	2	2:31	23.3	23.7	0.714	31.8	1.44	75.1†	85.9
	Aver.	.....	....	.....	.....	.....	.....	.....	.....
Cyril K.	Prelim.	11:31	....	.....	.....	.....	.....	.....	.....
12/18/15									
56.5 Kg.	1	12:31	22.7	22.3	0.740	31.9	0.927	.....	86.0
1.79 Sq. M.	2	1:31	21.5	22.6	0.698	28.0	0.927	.....	81.9
	3	2:31	22.2	23.5	0.686	29.5	0.927	.....	85.1
	Aver.	.....	....	.....	0.707	.....	.....	73.2	.....
Cyril K.	Prelim.	12:12	....	.....	.....	.....	.....	.....	.....
12/20/15									
56.9 Kg.	1	1:12	20.2	20.2	0.728	20.3	0.533	.....	72.5
1.79 Sq. M.	2	2:12	20.5	21.6	0.691	22.3	0.533	.....	72.6
	3	3:12	19.9	19.5	0.742	20.6	0.533	.....	67.3
	Aver.	.....	....	.....	0.720	.....	.....	68.4	.....
Cyril K.	Prelim.	11:42	....	.....	.....	.....	.....	.....	.....
12/22/15									
54.3 Kg.	1	12:42	19.7	19.6	0.731	21.4	0.60	63.6	64.2
1.75 Sq. M.	2	1:42	19.9	19.5	0.742	21.4	0.60	62.4	67.2
	3	2:42	19.0	19.0	0.729	20.8	0.60	61.5	64.5
	Aver.	.....	....	.....	.....	.....	.....	62.8	.....

* Calculations based on assumed D:N ratio of 3.62.
† Calculations based on assumed nonprotein R. Q. of 0.70.

Direct Calorimetry, Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
....	36.4	....	..	.....	..	..	..	....	.....	Basal; diabetes
51.5	36.4	?	12	0.760	18	67	15	1.25	38.4	Asleep 45 min.
56.6	36.4	68	24	0.814	18	52	30	1.22	37.5	Somewhat restless; awake
....	37.5	96	..	.....	..	..	..	....	.....	6 hrs. after dinner
77.8	37.8	99	32	0.732	..	..	..	....	.....	Restless
59.5	37.8	103	31	0.697	..	..	..	....	.....	Restless; 52 min. period
....	....	...	..	0.714‡	8	89	3	1.68	50.7	‡Aver. per hour
....	36.6	64	..	.....	..	..	..	....	.....	Basal, second fast day
53.2	36.4	72	20	0.775	15	65	20	....	.....	Reading 30 min.; asleep 10 min.
58.8	36.4	65	13	0.763	16	68	16	....	.....	Quiet; asleep 30 min.
....	....	....	..	.....	..	..	..	1.25	38.6	
....	37.1	60	..	.....	..	..	..	....	.....	At 6:30 a.m., ate protein 19, fat 18, carbo. 24
78.5	37.1	59	15	0.745	..	..	..	....	.....	Quiet; slept 5 min.
82.0	37.0	67	32	0.661	..	..	..	....	.....	Fairly quiet; awake
....	....	....	..	.....	21	79	0	1.44	45.7	Glucose in urine 6.76 gm. per hr.; D:N ratio 5.05
....	37.0	60	..	.....	..	..	..	....	.....	At 6:30 a.m., protein 26, fat 7, carbo. 0; sod. bicarb. at 9 a.m.
86.8	36.9	65	30	0.743	24	76	0	1.37	43.4	Slightly restless; read 50 min.
75.5	36.8	62	15	0.743	25	75	0	1.32	41.9	Much quieter; awake; did not read
....	....	....	..	.....	..	..	..	....	.....	Glucose in urine 5.24 gm. per hr.; D:N ratio 3.65
....	37.0	62	..	.....	..	..	..	....	.....	Basal; first fast day; sod. bicar. at 9 a.m.
77.2	36.8	63	15	0.750	..	..	..	....	.....	Reading quietly
75.6	36.7	61	8	0.689	..	..	..	....	.....	Reading 15 min.; quiet
74.3	36.5	59	19	0.682	..	..	..	....	.....	Fairly quiet
....	....	....	..	0.706	21	79	0	1.30	40.8	Glucose in urine 2.44 gm. per hr.; D:N ratio 2.63
....	36.3	....	..	.....	..	..	..	.. .	.....	Basal; third fast day
68.0	36.2	57	20	.....	..	..	..	....	.....	Quiet; reading
69.4	36.2	56	22	.....	..	..	..	....	.....	Quiet; reading
65.5	36.2	57	14	.....	..	..	..	....	.....	Very quiet
....	....	....	..	0.718	15	82	3	1.17	37.0	Urine glucose 1.18 gm. per hr.; D:N ratio 2.2
....	36.6	....	..	.....	..	..	..	....	.....	Basal; fifth fast day
58.8	36.5	59	14	0.724	20	75	5	....	.....	Reading; quiet
65.2	36.5	59	24	0.738	20	71	9	....	.....	Reading 30 min.; slightly restless
68.1	36.6	59	12	0.721	20	76	4	....	.....	Reading 30 min.; quiet
....	....	....	..	.....	..	..	..	1.16	35.9	Glucose in urine 0.92 gm. per hr.; D:N ratio 1.53

TABLE 5.—Data of Calorimeter—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Cyril K.	Prelim.	11:47	....	.....	.....	.....	.....	.....	.....
2/16/16									
45.8 Kg.	1	12:47	15.8	11.9	0.967	13.7	.....	.....	45.0
1.66 Sq. M.	2	1:48	15.3	12.7	0.877	14.1	.....	.....	47.0
	3	2:47	16.8	13.5	0.901	16.7	.....	.....	48.4
	Aver.	.....	....	.....	.....	.....	0.508	48.0	.....
Cyril K.	Prelim.	12:58	....	.....	.....	.....	.....	.....	.....
3/8/16									
48.2 Kg.	1	1:56	17.6	14.8	0.866	20.9	0.301	49.9	50.9
1.72 Sq. M.	2	2:58	17.5	14.9	0.854	21.2	0.301	50.1	52.6
	Aver.	.....	....	.....	.....	.....	.....	50.0	.....
Case 1 (Anna H.)	Prelim.	11:52	....	.....	.....	.....	.....	.....	.....
5/31/16									
32.5 Kg.	1	12:52	10.2	9.2	0.804	17.5	0.200	30.2	31.8
1.27 Sq. M.	2	1:52	9.5	8.2	0.840	15.6	0.200	27.2	29.5
	3	2:52	10.4	9.4	0.800	16.1	0.200	30.9	34.2
	Aver.	.....	....	.....	.....	.....	.....	.....	.....

December 22. Basal calorimeter observation. Food given in small amounts; alkali medication discontinued.

December 23. Improving steadily.

December 25. Patient was returned to Presbyterian Hospital. In a week he became permanently sugar-free, and without acetone bodies in his urine.

February 15, 1916, he returned to Bellevue for a calorimeter observation. That day he received 252 gm. of carbohydrate, 60 gm. of protein and 69 gm. of fat without showing sugar in the urine.

February 16, after being in the calorimeter he was given 270 gm. of carbohydrate, 44 gm. of protein and 11 gm. of fat in two and one-half hours. After this large meal he showed only a trace of sugar in his urine.

February 27. A peritonsillar abscess was accompanied by marked lowering of the carbohydrate tolerance.

March 7. Carbohydrate tolerance regained; blood sugar normal, 0.08 per cent. Patient weighed 47.7 kg. He was taking a diet containing 2,500 calories.

March 8. Put in the calorimeter and then sent to his home. Later he developed pulmonary tuberculosis, with high fever.

In February, 1917, the patient was improving somewhat. He died March 17, 1917, having been free from urinary glucose and acetone bodies for 125 days.

The patient was an ideal subject for metabolism study. He was intelligent and anxious to cooperate in all the necessary procedures. He was very quiet when in the calorimeter. The element of increased restlessness frequently observed in disease and suggested by Magnus-Levy[8] as a cause of the increased metabolism sometimes recorded, was therefore absent in this individual.

8. Magnus-Levy, A.: Respirationsversuche an diabetischen Menschen, Ztschr. f. klin. Med., 1905, **56**, 83.

—EXPERIMENTS—DIABETICS—(*Continued*)

Direct Calorimetry, Cal.	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M.	
....	34.9	....	..	.....	..	..	..	....	.....	Basal; bed
54.4	35.2	44	7	1.060	..	..	..	....	.....	Very quiet; reading
58.8	35.4	44	9	0.914	..	..	..	....	.....	61 min. period; very quiet
43.2	35.3	44	13	0.945	..	..	..	....	.....	59 min. period; very quiet; reading 50 min.
....	....	....	..	0.970	81	7	12	0.94	25.9	No glucose in urine
....	36.6	....	..	.....	..	..	..	....	.....	Basal
43.1	36.4	....	13	0.879	..	..	..	....	.....	Quiet; reading 15 min.; sleeping 15 min.
43.5	36.2	57	9	0.864	..	..	..	....	.....	Very quiet; reading whole hour
....	....	....	..	0.872	16	37	47	1.06	29.1	No glucose in urine
....	36.1	....	..	.....	..	..	..	....	.....	Basal; in bed
25.7	35.9	60	6	0.805	34	44	22	....	.....	Reading 45 min.
25.5	35.7	57	3	0.864	38	28	34	....	.....	Very quiet; asleep 30 min.
37.8	35.9	59	16	0.797	33	46	21	....	.....	Quiet; reading 10 min.
....	....	....	..	.....	35	39	26	0.91	23.2	

Summary.—This remarkable case may be reported in five successive periods, each sharply distinguished, and in a sixth period observed after an interval of two months. Table 6 represents the average daily figures obtained.

I. First Fasting Period.—The D:N in the urine during three days averaged 2.7 per day. The urinary nitrogen averaged 27.5 gm. daily, which is the highest level of nitrogen excretion ever recorded during fasting. It is threefold the quantity of nitrogen eliminated in ordinary fasting, and, therefore, brings this case of human diabetes in accord with the changes in protein metabolism noted in depancreatized and phlorhizinized dogs. During this period the blood-sugar was at its maximum (0.326 per cent.), beta-oxybutyric acid elimination reached 39.6 gm., and a low carbon dioxid tension in the blood betokened a considerable acidosis. Despite the administration, chiefly by intravenous injection, of between 53 and 114 gm. of sodium bicarbonate daily, the patient became increasingly drowsy, respirations were of the air hunger type, and he suffered from nausea.

II. Mixed Diet Period.—As fasting did not improve the patient's condition, he was given a diet of milk and eggs for four days, and on the third day his condition improved, he became less drowsy and there was less air hunger. After subtracting the carbohydrate ingested from the glucose eliminated in the urine, the D:N may be calculated as 1.9.

Although this indicates an oxidation of carbohydrate, the other metabolism factors of the pathologic complex show little improvement. Thus, the dietary contained 7.2 gm. of nitrogen daily and the urine 34.5 gm., an excess of 27.3 gm. above that contained in the food. The waste of 27.3 gm. of body nitrogen daily compares with a loss of 27.5 gm. daily during the fasting period immediately preceding. During this period of mixed diet the daily quantity of beta-oxybutyric acid eliminated increased to 56.5 gm. and the blood carbon dioxid tension fell to an average level of 22.1 mm. of mercury. It is difficult to find in the evidence presented by the metabolism data any cause for the improvement in the clinical condition.

TABLE 6.—METABOLISM OF CYRIL K.
Weight during Periods I-V, between 57.6 and 54.3 kg.; during Period IV, 45.8 kg.

Period	Date	Length of Period, Days	D:N	R. Q.	Urine		Blood		Calories per Sq. M. Surface	Variation from Normal, Per Cent.
					Nitrogen, Gm.	Beta-oxybutyric Acid, Gm.	Glucose in 100 C.c., Gm.	CO_2 Tension, Mm. Hg		
I. First fasting	1915 Dec. 8-10	3	2.7	.....	27.5	29.6	0.326	28.5		
II. Mixed diet	11-14	4	1.9	.....	34.5	56.5	0.312	22.1		
III. High protein-fat diet	15-17	3	3.9	0.687	37.0	77.8	.....	{19.6} {35.4}	44.1	+11
IV. Second fasting	18-21	4	2.7	0.714	16.3	45.7	0.166	44.4	38.9	— 2
V. Convalescence	22	1	1.1	0.734	18.3	10.9	0.181	52.8	35.9	—10
(Interval, 2 months)										
VI. Recovery	1916 Feb. 10	1	0.0	0.97	12.2	0.0	.....	....	25.4	—36

III. High Protein-Fat Diet Period.—During a period of three days the patient was given a diet of protein and fat, and a D:N ratio of 3.9 was determined. Although no experimental data are available to show why this ratio is higher than 3.65, yet it is possible that the extra sugar may have been derived from a reduction in the quantity of sugar in the body, as would have been indicated by a lowering of the level of blood-sugar. The quantity of "extra sugar," or that eliminated in excess of a D:N ratio of 3.65, may be calculated as being 57 gm. during the three-day period. The patient weighed 57 kg., so that a fall of 0.1 per cent. in the quantity of blood sugar would explain the origin of the "extra sugar." The diet contained an average of 13.7 gm. of nitrogen daily, the urine 37.0 gm., a difference of 23.3 gm., or almost as great a loss of body nitrogen as during the two preceding periods. On the second day of this diet the patient manifested marked clinical improvement, sat up in bed and said he felt much better than two days

before, yet on this day the carbon dioxid tension in the blood fell to its lowest level of 19.6 mm. of mercury, and 75 gm. of beta-oxybutyric acid were eliminated. On the third day, however, the carbon dioxid tension reached 35.4 mm., a level which is more in accord with the actual improvement of the patient. During this period an average of 55 gm. of sodium bicarbonate were given daily.

The beta-oxybutyric acid excretion averaged 77.8 gm. On the two days in which calorimeter investigations were conducted the results may be computed to show how much of the total metabolism of fat reached beta-oxybutyric acid as its terminal stage. When fat is thus oxidized it is theoretically possible for 21.7 per cent. of the quantity of carbon dioxid ordinarily eliminated in the respiration to remain unoxidized in the form of beta-oxybutyric acid. Remembering this, one may make the computation shown in Table 7.

TABLE 7.—BETA-OXYBUTYRIC ACID ELIMINATION

The quantity of beta-oxybutyric acid eliminated per hour was slightly in excess of the quantity derivable from the fat metabolism of the time.

Date	Urine			Calories	CO_2, Gm.	Nonprotein CO_2, Gm.	Theoretical Beta-oxybutyric Acid from Fat, Gm.*
	Nitrogen, Gm.	D:N	Beta-oxybutyric Acid, Gm.				
12/15	1.34*	3.97	3.13	81.9	24.2	18.9	3.09
12/16	1.44*	4.01	2.95	76.4	23.7	18.1	2.96

* Eliminated per hour during calorimeter period.

It is apparent from Table 7 that on one of the two successive days the hourly elimination of beta-oxybutyric acid was slightly greater than the quantity derivable from the fat metabolism of the hours spent in the calorimeter. The slight excess may have been due to a slightly greater average of fat metabolism during the twenty-four-hour period than that observed during the calorimeter period, or it may have been due to an origin of beta-oxybutyric acid from those amino-acids which yield it. A considerable origin of beta-oxybutyric acid from the latter source is not indicated.

The picture presented during this period is one in which all the glucose derivable from protein and all the beta-oxybutyric acid formed as an end-product of the oxidation of fat is completely eliminated in the urine. Though Magnus-Levy[9] computed such results for a diabetic and comatose youth, the actual demonstration of this condition is here presented for the first time.

9. Magnus-Levy, A.: Die Acetonkörper, Ergebn. d. inn. Med., 1908, **1**, 385.

The Respiratory Quotient.—An analysis of the diabetic respiratory quotient has already been presented in one of this series of papers.[10] During the period of a high protein-fat diet it is evident that the metabolism was highly abnormal. Only protein and fat were oxidized, and these only partially. It has been shown that when the D : N ratio is 3.65, the protein respiratory quotient becomes 0.632 instead of 0.80 normally, and when beta-oxybutyric acid is produced as the end-product of fat metabolism, the calculated respiratory quotient of fat falls to 0.669 instead of being 0.707, its normal value.

Were this the whole story, one should find agreement between the respiratory quotient as calculated from the end-products of metabolism during the period of severe diabetes and that actually found. Thus, on December 16 when the diabetes was complete, one might calculate the respiratory quotient as follows:

	Respired Gases		
	O_2 Liters	CO_2 Liters	R. Q.
If the D : N were 3.65, then 1.44 gm. N in urine =	4.58	2.91	0.63
If 18.1 gm. nonprotein CO_2 be derived from fat less unoxidized beta-oxybutyric acid,	13.77	9.21	0.67
	18.35	12.12	0.66

The respiratory quotient was actually 0.715, and, as a matter of fact, quotients as low as 0.66 have not been reported in trustworthy experiments on the basal metabolism in diabetes. It is evident that some accessory factors must come into play. It is highly probable that the interaction between acid formation and bicarbonate neutralization plays an important rôle in diabetes. Thus, if beta-oxybutyric acid formed from fat neutralizes sodium bicarbonate, the diabetic respiratory quotient for fat would be 0.715 instead of 0.669. Again, if the acid were neutralized with ammonia instead of with bicarbonate, it would have been at the expense of ammonia which normally would have combined with carbon dioxid in urea formation. The carbon dioxid would tend to be liberated in the respiration and the quotient would be increased.

Under certain conditions of recovery from the diabetic condition, respiratory quotients of 0.80 during fasting have been noted by Joslin,[11] and this has been attributed to the oxidation of beta-oxybutyric acid, which gives a respiratory quotient of 0.889. It should be noted, however, that if sodium beta-oxybutyrate be oxidized to bicarbonate of sodium, the respiratory quotient of the substance would be only 0.667. The unknowable interplay of factors which govern the finer details of

10. Lusk, G.: Clinical Calorimetry, Paper 8. On the Diabetic Respiratory Quotient, THE ARCHIVES INT. MED., 1915, **15**, 939.

11. Joslin, E. P.: Treatment of Diabetes Mellitus, New York, 1916, p. 96.

the respiratory quotient in diabetes prevents its precise interpretation. It is sufficient to bear in mind, however, that the quotient of 0.69, which is frequently found in total diabetes, indicates the oxidation of fat with the neutralization of sodium bicarbonate by the beta-oxybutyric acid formed. The following summary compares the respiratory quotients obtained under different conditions in this laboratory:

	D:N	R. Q.	Nonprotein R. Q.
Diabetic man, Cyril K.	3.97	0.687	0.699
Diabetic man, Gerald S.	3.50	0.697	0.700
Phlorhizinized dog	3.54	0.687	0.704

December 15 the nonprotein respiratory quotient of Cyril K. was 0.699, which is sufficiently close to 0.715 to indicate that the oxidation of fat proceeded in such a manner that some carbon dioxid was driven off from combined bicarbonate in the blood. December 16, under essentially the same condition of diabetes in its most intense form, the nonprotein respiratory quotient was 0.743. The alveolar tension of carbon dioxid was taken immediately before and immediately after the respiration experiment, and it fell from 0.21 mm. of mercury to 0.15 mm. This suggests an increased neutralization of acid by the blood with expulsion of carbon dioxid. It is this extra elimination of carbon dioxid which may play some part in this otherwise inexplicably high nonprotein respiratory quotient.

Grafe[12] calculated that if all the nitrogen of protein metabolism were eliminated as ammonia, the quotient would rise from the normal of 0.80 to 0.88. When, in our experiments, a correction of the respiratory quotient of protein was attempted because of the large elimination of ammonia, this has not increased the R. Q. more than 0.01.

The total heat production during this period of complete diabetes presents some interesting aspects. The method of calculating the heat produced from protein metabolism in severe diabetes, as described by Lusk,[13] has here been followed.

When the D:N ratio has fallen below 3.65, the effect on the respiratory quotient and the heat value of protein has been calculated by making deductions for the separate periods, remembering that each gram of glucose derived from protein would normally be associated with

Heat production	3.692 cal.
Oxygen absorption	1.067 gm.
Carbon dioxid elimination	1.467 gm.

It should be further remembered that when ammonia is converted into urea by union with carbon dioxid, heat is absorbed in the reaction. When abnormally large amounts of ammonia are eliminated in the urine, this heat

12. Grafe, E.: Zur Kenntniss des Stoffwechsels im protrahierten Hungerzustande, Ztschr. f. physiol. Chem., 1910, **65,** 48.

13. Lusk, G.: Jour. Biol. Chem., 1915, **20,** 600.

would be liberated in the body and not in the urea of the urine. Several calculations of this kind showed that such additional heat did not exceed 1 calory an hour.

The ordinary method for calculating the heat value of fat remains unchanged in spite of the abnormal production of beta-oxybutyric acid. For a liter of oxygen when used to oxidize beta-oxybutyric acid gives a heat value of 4.848 calories, if the figure, 4.69 calories per gram given by Emery and Benedict,[14] is adopted as the heat value of this substance. When fat itself is completely oxidized, the heat value of a liter of oxygen is 4.686, but when 100 gm. are oxidized, leaving a residue of 36 gm. of beta-oxybutyric acid, the heat value of a liter of oxygen is reduced to 4.654, a difference of 0.7 per cent.

In a former paper of this series by Allen and Du Bois[1] the question of the level of total metabolism in diabetes mellitus was discussed at length and need here be considered only in relation to the specific case. It has long been definitely known that an increased protein metabolism increases the heat production. Rubner[15] was the first to advance the idea that the increased heat production in experimental diabetes was due to an increased metabolism. Even though a large amount of the energy present in protein be eliminated in the urine as glucose, still the specific dynamic action of protein is present when it is ingested in diabetes.[16]

The total metabolism of Cyril K. during the period of high protein and fat ingestion was found to be 15 and 7 per cent. above the normal standard of metabolism per square meter of surface given in Paper 13 of this series. The high protein metabolism might sufficiently explain this increase.

The analysis of this factor may be accomplished in the following manner: If one assume that the usual normal excretion of protein nitrogen is 0.5 gm. per hour, one may calculate how much in excess of this the protein metabolism was during the hours of calorimeter investigation. Since Aub and Du Bois[17] find that in man, when 100 calories in protein are metabolized, the total heat production increases by 76.4 calories, it is possible to compute by what increment the extra metabolism of protein would increase the heat production. Such a calculation is presented in Table 8.

The first two observations on Cyril K. were made six hours after taking food. It is questionable whether the small amount ingested

14. Emery, A. G., and Benedict, F. G.: The Heat of Combustion of Compounds of Physiological Importance, Am. Jour. Physiol., 1911, **28**, 301.

15. Rubner, M.: Die Gesetze des Energieverbrauchs bei der Ernährung, Leipzig, 1902, p. 370.

16. Lusk, G.: Loc. cit., note 6, p. 555.

17. Aub, J. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 21, THE ARCHIVES INT. MED., this issue.

would have much effect in stimulating metabolism at the time of observation.

It appears from this calculation that the extra heat production noted in Cyril K. was due to the extraordinarily high protein metabolism, and that with the elimination of that factor the metabolism more nearly approximated that to be expected in a somewhat emaciated individual.

The *prognosis,* as based on the laboratory findings of this case, seemed at this point to be most unfavorable and was so pronounced by Allen and by Lusk, while Joslin, who saw the patient at the same time, stated that he would recover.

IV. Second Fasting Period.—Following the period of high protein diet, a second fasting period was initiated, which extended over four days. The D:N ratio was 2.7, as during the first fasting period. There

TABLE 8.—SPECIFIC DYNAMIC ACTION OF EXCESSIVE PROTEIN DESTRUCTION (CYRIL K.)

Date	Urinary Nitrogen in Excess of Normal Basal per Hour	Extra Calories Due to Specific Dynamic Action (Extra N × 26.5 × 0.764)	Total Calories per Hour	Total Calories Minus Calories of Specific Dynamic Action	Calories (minus Calories of Specific Dynamic Action) per Sq. M. per Hour	Per Cent. Average Normal
1915						
12/15	0.82	16.8	81.9	65.1	36.4	— 8
12/16	0.98	18.8	76.4	57.6	32.2	—19
12/18	0.42	8.5	73.2	64.7	36.1	— 9
12/20	....	....	66.3	....	37.0	— 7
12/22	....	....	62.8	....	35.9	—10

were three distinct factors which showed improvement over the fasting period of the week before: (a) a lower protein metabolism; (b) a lower level of blood sugar; (c) a higher carbon dioxid tension of the blood. The elimination of beta-oxybutyric acid, however, did not markedly decrease until the fourth fasting day. The patient showed steady improvement throughout this period, read all day and was free from drowsiness.

V. Convalescent Period.—Following the period of four days of fasting, during which the D:N was 2.7, this ratio suddenly broke to 1.1, the quantity of beta-oxybutyric acid eliminated fell to 11 gm., and the respiratory quotient rose in response to the change in metabolism. Although clinically the condition of the patient had shown constant improvement, yet this day was the first to herald the overthrow of all features of the pathologic metabolism. Within a week he became permanently free from glycosuria and from acetonuria.

It is interesting to note that the excretion of beta-oxybutyric acid decreased before the fall in the D:N ratio, as appears in Table 9.

It may reasonably be questioned whether there could possibly have been an increase in the number of sugar molecules liberated in the metabolism of protein on December 21, such as to have been the cause of the improvement in the oxidation of fat, as evidenced by the fall in the quantity of beta-oxybutyric acid excreted. On the other hand, it may well be that the improvement in the conditions for the oxidation of fat may have reduced the acidosis to such an extent as to have beneficially affected the oxidation of glucose. These latter relations have been set forth in a series of papers by Murlin.[18]

Woodyatt[19] has recently stated that the decrease of acidosis in fasting, emaciated diabetics may, in part, be due to the fact that the metabolism may be solely at the expense of protein. Our observations

TABLE 9.—Showing Fall in Beta-Oxybutyric Acid Before Fall in D:N Ratio

Period	Date	D:N	Beta-oxybutyric Acid
IV	12/19*	2.65	56.84
	12/20*	2.44	41.17
	12/21*	2.65	36.21
V	12/22*	1.12	10.95

* Fasting.

do not corroborate this view, for the highest amount of heat from protein yielded during periods of basal metabolism in severe diabetes has never exceeded 23 per cent. of the total heat production.

During the period of high protein-fat diet and of high acidosis the quantity of *sodium chlorid* was less in the urine than in the diet, whereas the opposite conditions obtained during the following period of fasting which resulted in the clearing up of the acidosis.

VI. Recovery.—After an interval of two months the patient returned to Bellevue Hospital and was again placed in the calorimeter for the determination of his basal metabolism. The day before he had partaken of a diet containing:

Protein	60 gm.
Carbohydrate	252 gm.
Fat	6 gm.

18. Murlin, J. R., and Kramer, B.: Pancreatic Diabetes in the Dog, Jour. Biol. Chem., 1916, **27**, 481.

19. Woodyatt, R. T.: Acidosis in Diabetes, Jour. Am. Med. Assn., 1916, **66**, 1910.

There was no sugar in the urine. The determination of the basal metabolism revealed a respiratory quotient of 0.92 and a nonprotein respiratory quotient of 0.97. These results showed that this man was now deriving his energy, 62 per cent. from carbohydrate, 31 per cent. from protein and 6 per cent. from fat. This astonishing result shows that Cyril K., who two months before had been completely diabetic, was now able to derive two-thirds of his basal requirement for energy from the oxidation of carbohydrate.

Before the onset of diabetes the weight of the patient had been approximately 73.6 kg. His minimal recorded weight as the result of the Allen fasting treatment was 45.8 kg., a loss of 27.8 kg., or 38 per cent. The normal basal metabolism of a man weighing 73.6 kg. and having a height of 188 cm. would have been 79 calories. This contrasts with an actual production of energy amounting to only 43 calories per hour when he was reduced to a weight of 45.8 kg. His heat production was therefore only 55 per cent. of what it would have been had he been of his normal weight.

The results calculated from Case 1 may be compared with those of this patient as in Table 10.

TABLE 10.—COMPARISON OF RESULTS IN CASE 1 WITH THOSE OF CYRIL K., CASE 3

Case	Height, Cm.	Original Weight, Kg.	Lowest Weight, Kg.	Lowest Heat Production in Per Cent. of the Original Normal	Variation in Per Cent. from the Normal per Sq. M. of Surface when Heat Production Was Lowest
1	169	62	32.5	40	—37
3	188	74	45.8	55	—35

After three weeks Cyril K. gained 3.5 kg. in weight, and his metabolism was found to be 27 per cent. below the normal for his weight and height, instead of 35 per cent. below when his emaciation was more extreme.

These experiments on individuals indicate how a community may long support itself on restricted rations.

SUMMARY

Three cases of diabetes studied in the respiration calorimeter are reported.

Case 1.—A diabetic woman through prolonged fasting had been brought to a level of metabolism 37 per cent. below the standard level for her height and weight, a metabolism which was only 40 per cent.

of the original normal value before the initiation of fasting. This is the lowest level of metabolism ever recorded.

Case 2.—A patient with a mild case of diabetes, whose urine was free from sugar, became suddenly and completely diabetic on the administration of a high protein-fat diet, and, on fasting, rapidly regained his former tolerance for sugar.

Case 3.—An acute case of complete diabetes which, in high protein metabolism and in high D:N ratios, resembled experimental diabetes in animals. When given meat and fat, the patient not only excreted all the sugar derivable from protein, but he also excreted all the beta-oxybutyric acid derivable from the fat metabolism of the time. Two months later when the metabolism was 35 per cent. below the normal for his height and weight, two-thirds of the total calories were derived from carbohydrate. The case has afforded an opportunity for the discussion of many of the fundamental facts concerning diabetes mellitus.

477 First Avenue.

CLINICAL CALORIMETRY

TWENTY-FIFTH PAPER

THE WATER ELIMINATION THROUGH SKIN AND RESPIRATORY PASSAGES IN HEALTH AND DISEASE*

G. FABIAN SODERSTROM AND EUGENE F. DU BOIS, M.D.

NEW YORK

1. Introduction.
2. The Sources of Error in Technic.
3. Review of the Literature.
4. Methods Used.
5. Water Elimination of Normal Men Under Standard Conditions.
6. Water Elimination of Patients Under Similar Conditions.
7. Summary and Conclusions.

INTRODUCTION

Few clinicians realize the importance of water in the metabolism, and few investigators appreciate the large errors in its measurement. Apparently, there is nothing easier to measure, and this has led many to publish results without careful controls as to accuracy. As a matter of fact, the technic of determining the water of vaporization is exceedingly difficult and there are few things more laborious than the establishment of the water balance of a patient.

Rubner has pointed out that a starving animal can lose practically all of his glycogen and fat and half of his body protein. If he loses about 10 per cent. of the water of his body he dies. In the clinic few attempts are made to measure the water balance of patients whose tissues are becoming dried on account of insufficient water intake in comparison with an increased output. With edematous patients it is the custom to measure the urine and the fluids of the food with the idea of determining the gain or loss of water to the body. Such measurements are very incomplete. as will be shown by the accompanying example of a true balance sheet (Table 1).

Clinicians allow the nurses to make a large error in neglecting the water content of the so-called *solid* foods. Let us take, for example, the following meal: A small dish of farina, a boiled potato, a portion of tomato and lettuce salad, a small dish of junket and an apple. This is a supper that might well be given a nephritic patient, but it contains about 690 gm. water, something over 23 ounces.

* Submitted for publication Jan. 11, 1917.

* From the Russell Sage Institute of Pathology, in affiliation with the Second Medical Division, Bellevue Hospital.

TABLE 1.—ILLUSTRATING WATER BALANCE

	Gm.	
Water Intake:		
Drinking water	800	
Water in coffee, milk, soup	580	
Water in "solid foods"	720	
H_2O from oxidation of 100 gm. protein	41	
H_2O from oxidation of 110 gm. fat	118	
H_2O from oxidation of 244 gm. carbohydrate	135	
		1,894
Water Output:	Gm.	
Water in urine	750	
Water in feces	300	
Water vaporized through skin and respiratory passages	700	
		1,750
Plus balance to body		144
Gain in body weight		100

It is the purpose of the present paper to give some idea as to the amount of water lost from the body in vaporization, and to call attention to this neglected factor in the total output. We can try to estimate the so-called *insensible* perspiration by weighing the patient every day and measuring everything taken and excreted. More accurate determinations can be made in a few cases in respiration chambers. Absolutely accurate determinations cannot be made at present, and it seems advisable to take up this point in detail before reviewing the literature of the subject.

Alcohol Checks.—It has been the policy of the Russell Sage Institute of Pathology to publish each year all the alcohol checks made with the calorimeter (Table 2). This enables other investigators to satisfy themselves as to the accuracy of the apparatus at any given time during the experimental season. Occasionally, there will be an error as great as 2 per cent. in some of the measurements. The average errors for the season of 1915-1916 are as follows:

	Per Cent.
Heat	+0.63
Oxygen	−0.25
Carbon dioxid	−0.42

Respiratory quotient 0.665 instead of the theoretical 0.6666. This shows that the calorimeter is still extraordinarily accurate. The usual error of +2.5 per cent. in measuring the water elimination will be discussed later. It is interesting to study the results in the check of April 3, when about one-quarter of the customary amount of alcohol was burned. The measurement of oxygen and carbon dioxid was surprisingly good, but the method of direct calorimetry gave an error of +2.5 calories in three hours. The large calorimeter was never intended to measure a heat production as low as 19 calories an hour, but even for such small amounts, using the method of indirect calorimetry, it compares favorably with any other respiration chamber as yet constructed.

THE SOURCES OF ERROR IN TECHNIC

It is a very simple matter to measure the water vapor entering and leaving a respiration chamber in which a man or a part of his body is confined. The difference would represent the water vaporized from the body were it not for the fact that water clings to the walls and to the contents of every experimental cabinet. Surprisingly few investigators have taken the trouble to see just how much could be lost or gained in this manner. Stohman[1] called attention to the amount of water that could be absorbed by wood and painted metal. Atwater and Benedict[2] tested the accuracy of the water determination of the Middletown calorimeter, and later the question was discussed in detail by Benedict, Riche and Emmes[3] and by Benedict,[4] who found that large amounts of water vapor could be removed from calorimeter walls and from clothes, bedding and other materials contained within them.

In Papers 2 and 11 of this series it was shown by means of alcohol checks that the Sage calorimeter measured very accurately the oxygen, carbon dioxid and heat, but gave an average error of more than 3 per cent. in the determination of the water produced by the flame. The amount of alcohol usually burned each hour gives off about as much heat and carbon dioxid as a man and consumes about the same amount of oxygen, but produces somewhat less than half the water vaporized by most of the subjects. As a result, the air in the box becomes drier and drier and the water vapor deposited on the tinned walls of the calorimeter, on the copper cooling pipes, on the glass windows and the small wooden parts of the air thermometers, is more or less completely removed as the test progresses. During the first few hours of the experiment there may be a plus error of 0.5 to 1.0 gm. an hour, but later it seldom exceeds half a gram. When the wooden bed, pillow, folded sheet, night-shirt, socks and pajamas are in the calorimeter, astonishing amounts of water can be absorbed or given off, depending on the changes in the relative humidity of the air. In order to demonstrate this, three experiments were made. Nov. 17, 1916, the bed and clothing were placed in the calorimeter, the alcohol lamp was adjusted to burn the usual amount of alcohol per hour, and an arrangement was made by which known amounts of water could be dripped on a piece of muslin about a foot square, tacked on a small wooden frame. The total water vapor formed was estimated by adding the

1. Stohman: Landwirthschaftliche Versuchsstationen, 1876, **19,** 81 and 159.
2. Atwater, W. O., and Benedict, F. G.: A Respiration Calorimeter, Carnegie Institution of Washington, Pub. 42, 1905.
3. Benedict, F. G., Riche, J. A., and Emmes, L. E.: Control Tests of a Respiration Calorimeter, Am. Jour. Physiol., 1910, **26,** 1.
4. Benedict, F. G.: A Comparison of the Direct and Indirect Determination of Oxygen Consumed by Man, Am. Jour. Physiol., 1910, **26,** 15.

TABLE 2.—Alcohol Checks—

Date	Hour	Heat				Oxygen		
		Alcohol Burned, Gm.*	Theory, Cals.	Found, Cals.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.
10/29/15	1	12.70	81.2	81.7	+0.6	22.9	24.8	+8.7
	2	12.34	78.9	79.4	+0.6	23.2	22.9	−1.4
	3	12.77	81.7	80.1	−2.0	24.1	23.6	+2.0
	4	12.10	77.4	78.7	+1.7	22.8	23.3	+2.2
Average	...	.....	79.8	80.0	+0.2	23.5	23.8	+1.3
12/13/15	1	11.17	73.5	68.8	−6.0	21.6	21.6	±0.0
	2	10.44	68.7	69.1	+0.6	20.2	20.2	±0.0
	3	10.38	68.3	69.7	+2.0	20.1	20.4	+1.5
Average	...	.....	70.2	69.2	−1.3	20.6	20.7	+0.5
1/19/16	1	11.96	78.7	79.5	+1.0	23.2	22.9	−1.3
	2	12.42	81.7	80.7	−1.2	24.1	25.3	+5.0
	3	12.37	81.4	80.7	−0.8	24.0	24.2	+0.8
Average	...	.....	80.6	80.3	−0.3	23.8	24.1	+1.2
1/21/16	1	11.59	76.3	78.4	+2.7	22.5	22.6	+0.4
	2	11.44	75.3	76.1	+1.0	22.2	22.4	+0.9
	3	11.31	74.4	77.0	+3.5	21.9	21.5	−1.8
Average	...	.....	75.3	77.2	+2.4	22.2	22.2	±0.0
2/18/16	1	11.92	78.4	77.8	−0.7	23.1	22.5	−2.6
	2	11.80	78.2	77.9	−0.4	23.0	23.0	±0.0
	3	11.26	74.1	75.2	+1.5	21.8	21.2	−2.7
Average	...	.....	76.9	77.0	+0.1	22.6	22.2	−1.8
2/25/16	1	11.82	77.8	77.5	−0.4	22.9	22.5	−1.7
	2	11.47	75.5	76.1	+0.8	22.2	22.3	+0.4
	3	11.72	77.2	78.0	+1.0	22.7	22.5	+0.8
Average	...	.....	76.8	77.2	+0.5	22.6	22.4	−0.9
4/ 2/16	1	2.69	17.7	19.1	+7.9	5.21	4.93	−5.4
	2	2.49	16.4	20.4	+24.4	4.82	5.15	+7.0
	3	3.37	22.2	24.5	+10.5	6.53	6.33	−3.1
Average	...	.....	18.8	21.3	+13.3	5.52	5.48	−0.7
4/14/16	1	12.62	83.1	83.3	+0.2	24.5	24.3	−0.8
	2	12.35	81.3	81.1	−0.2	23.9	23.3	−2.5
	3	12.26	80.7	81.3	+0.5	23.8	23.5	−1.3
Average	...	.....	81.7	81.9	+0.2	24.1	23.7	−1.6
4/17/16	1	14.07	174.2	84.4	+0.3	51.3	24.8	−0.2
	2	12.41		90.3			26.4	
	3	13.28	87.4	87.8	+0.5	25.7	25.4	−1.1
Average	...	.....	87.2	87.5	+0.3	25.7	25.5	−0.8
Total.....	...	.....	2,021.7	2,034.6	+0.63	595.3	593.8	−0.25

water produced by the alcohol flame to the water dripped into the box each hour. The results are shown in Table 3, and it will be seen that 24 to 28 gm. of water were lost per hour. The method of dripping water was rather crude, and much water must have been retained by the wooden frame. Even so, it was evident that the bed and clothing, which had been placed in the box when very dry, absorbed a great deal of water as the humidity rose rapidly. After this experiment was over, still more water was vaporized, the air almost

—SEASON 1915-1916

Carbon Dioxid			Water			R. Q.
Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, 0.667
21.9	22.1	+0.9	14.7	15.4	+4.8	0.648
21.3	21.4	+0.4	14.3	14.8	+3.5	0.678
22.0	21.5	−2.2	14.8	14.8	±0.0	0.664
20.9	21.0	+0.5	14.0	14.7	+0.5	0.659
21.5	21.5	±0.0	14.4	14.9	+3.4	0.662
19.8	19.7	−0.5	12.9	12.9	±0.0	0.664
18.5	18.3	−1.0	12.1	12.4	+2.4	0.660
18.4	18.4	±0.0	12.1	12.3	+1.7	0.657
18.9	18.8	−0.5	12.4	12.5	+0.8	0.660
21.2	21.0	−0.9	13.9	14.0	+0.7	0.668
21.6	22.2	+2.7	14.4	14.6	+1.4	0.640
22.0	21.6	−1.8	14.4	14.1	−2.0	0.647
21.6	21.6	±0.0	14.2	14.2	±0.0	0.652
20.6	20.4	−0.9	13.5	13.8	+2.2	0.658
20.3	20.1	−0.9	13.3	13.5	+1.5	0.651
20.1	20.0	−0.5	13.1	13.5	+3.0	0.674
20.3	20.2	−0.5	13.3	13.6	+2.2	0.661
21.2	20.9	−1.4	13.9	13.9	±0.0	0.676
21.1	21.0	+0.4	13.8	14.1	+2.1	0.664
20.0	19.9	−0.5	13.1	13.3	+1.5	0.682
20.8	20.6	−0.9	13.6	13.8	+1.4	0.674
21.0	20.6	−1.9	13.7	14.0	+2.2	0.664
20.4	20.4	±0.0	13.3	13.7	+3.0	0.666
20.9	20.8	−0.5	13.6	13.9	+2.2	0.672
20.8	20.6	−0.9	13.5	13.9	+3.0	0.667
4.78	4.61	−3.6	2.98	3.77	+26.0	0.680
4.42	4.69	+5.6	2.89	3.63	+25.0	0.662
5.98	5.99	±0.0	3.93	4.16	+ 6.0	0.688
5.06	5.07	∓0.0	3.26	3.85	+18.0	0.677
22.4	22.3	−0.4	14.7	15.0	+2.0	0.669
21.9	21.7	−0.9	14.3	14.5	+1.4	0.677
21.8	21.5	−1.3	14.2	14.5	+2.1	0.667
22.0	21.8	−0.9	14.4	14.7	+2.0	0.671
47.0	23.0	+0.6	30.7	15.4	+4.2	0.676
	24.1			16.6		0.665
23.6	23.6	±0.0	15.4	15.8	+2.6	0.672
23.5	23.6	+0.4	15.4	15.9	+3.2	0.672
545.1	542.8	−0.42	358.0	367.1	+2.51	Av. 0.665

* In all tests the solution contained 92.92 per cent. by weight of ethyl alcohol.

saturated and allowed to stand this way all night. The next morning the calorimeter was opened and the muslin on its wooden frame placed on a copper plate over the chimney of the alcohol lamp. The lamp was lighted, and during the preliminary period of an hour and the first experimental period of thirty minutes, water was dripped on the muslin, raising the humidity to 60 per cent., at which point there appeared the first dew on the polished pipe of the ingoing water

at a temperature of 15.9 C. The dripping of water was then discontinued and from this time the alcohol flame was the only source of water except for the bed and clothing and wall of the box. The rate of ventilation was then increased until the relative humidity had fallen to 27 per cent. The large amounts of water removed from the calorimeter can be seen in Table 3. December 4, a complete alcohol check was made, but in addition, 20 c.c. extra water was dripped each hour on a small piece of asbestos in an enamel-ware plate over the lamp chimney. The amount of water recovered was from 1.5 to 2.6 gm. an hour less than the total vaporized. The bed and clothing, which had been exposed to comparatively dry air all night, continued to absorb some moisture for several hours after they were exposed to a greater, but uniform, humidity. In this experiment the average error in the water measurement was 6.7 per cent. It could perhaps be reduced to half of this if great care were taken to maintain an even humidity in the calorimeter room all night. This is difficult, but it is now being attempted.

TABLE 3.—Moisture Tests

Length of Period, Minutes	Total H_2O Formed or Dripped into Calorimeter, Gm.	H_2O Removed, Gm.	Errors, Gain or Loss, Gm.	Relative Humidity at End of Period	Remarks
Nov. 17	....	....	.....	38	Water dripped into box
60	53.0	25.0	−28.0	45	
60	50.0	26.0	−24.0	44	Water dripped into box
Nov. 18	....	....	.....	54	
30	30.0	16.0	−14.0	60	Water dripped into box
30	8.0	19.0	+11.0	57	No extra water
30	9.0	18.0	+ 9.0	54	No extra water
60	16.0	40.0	+24.0	33	No extra water
60	17.0	30.0	+13.0	29	No extra water
60	17.0	27.0	+10.0	27	No extra water
Dec. 4	....	....	.....	36	
60	33.9	32.4	− 1.5	37	20 c.c. extra water dripped into box each hour
60	33.6	30.9	− 2.7	28	
60	33.2	30.6	− 2.6	26	
	100.6	92.9			

The Sage calorimeter is probably much better adapted for the accurate determination of water vaporized than any other respiration chamber except the Middletown calorimeter, which was used for periods of several days. Even so, it is doubtful if it is much more accurate than 10 per cent. under ordinary conditions.

REVIEW OF THE LITERATURE

In reading over the many publications on the subject of water vaporization we must bear in mind the large technical errors found in all types of apparatus. Some investigators took the trouble to weigh the clothing of their subjects before and after the experiment, but could not weigh the experimental chamber and its furniture. Some made the error of drying the cabinet before an experiment, not realizing that water could be lost with a rising humidity. Some have even expressed their results in six significant figures, when it is doubtful if the second figure was accurate.

The older work on vaporization is well reviewed by Rubner,[5] Magnus-Levy[6] and Tigerstedt.[7] In 1866 Pettenkofer and Voit[8] found that the water elimination of a fasting man was 814 to 829 gm. a day. Voit's pupil, Rubner, made a very thorough study of the question, and with his assistants published a series of papers which are of great importance. Their value is increased by the fact that they were produced in the same laboratory with comparable experimental methods. Rubner[9] first studied guinea-pigs and dogs, using a small Pettenkofer-Voit chamber and an air calorimeter. He found that animals gave off much more water in dry than in moist air, a drop in the relative humidity from 69 to 31 per cent. increasing the water elimination from skin and lungs twofold or threefold. Water elimination in guinea-pigs increased as the temperature of the air was raised above 15 C.; in dogs it increased with temperatures above 7 C. When the dogs were given meat, thus increasing the heat production, the water elimination was not affected when the surrounding air was cool, but was markedly increased when the air was warm. Rubner found that for different animals the water elimination was not proportional to surface area, but was nearly proportional to body weight. He concludes, also, that variations in the humidity of the air do not affect the metabolism of protein and fat, and cause no significant change in the total heat production. Increasing moisture in the air diminishes the heat loss through vaporization, but correspondingly increases the heat loss through radiation and conduction.

---

5. Rubner, M.: Die Gesetze des Energieverbrauchs bei der Ernährung, Leipzig, 1902; Lehrbuch der Hygiene, Leipzig, 1907.

6. Magnus-Levy, A.: In von Noorden's Handbuch der Pathologie des Stoffwechsels, Berlin, 1906, **1.**

7. Tigerstedt, R.: Wärmeverlust des Körpers, in Nagel's Handbuch der Physiologie des Menschen, Braunschweig, 1909, **1,** 581.

8. Pettenkofer, M., and Voit, C.: Untersuchungen über den Stoffverbrauch des normalen Menschen, Ztschr. f. Biol., 1866, **2,** 478.

9. Rubner, M.: Die Beziehung der atmosphärischen Feuchtigkeit zur Wasserdampfabgabe, Arch. f. Hyg., 1890, **11,** 137; Stoffzerzetzung und Schwankungen der Luftfeuchtigkeit, ibid., p. 243; Thermische Wirkungen der Luftfeuchtigkeit, ibid., p. 255.

TABLE 4.—Water Elimination At 15 C.

	Weight, Gm.	H_2O per Kg. per Day	Percentage of Calories Lost in Vaporization
Man	70,000	12.6	22.9
Dog	30,000	12.2	20.5
Dog	4,000	11.5	9.0
Guinea-pig	550	11.3	6.5

Cramer[10] found that salt was excreted by the skin even when the subjects were at rest in a room at low temperature and concluded that there was a continual secretion of insensible sweat. Nuttall[11] found that when a naked man was placed in a cabinet at a temperature of 29 C., changes in the humidity between 12 and 63 per cent. had little influence on the amount of water removed by the apparatus. Wolpert[12] found that light work scarcely increased the water elimination above the resting values, but that heavy work caused a large increase. He found that the variations in the humidity of air next to the body are limited by the clothing and are not as great as the variations in the outside air. When the air temperature was between 15 and 35 C., the wind from a fan diminished the water loss from the body; above and below these points it increased the vaporization. Laschtschenko[13] demonstrated that the drinking of two liters of water had no effect on the amount eliminated through skin and respiratory passages. Rubner[14] made some interesting determinations of the water eliminated

10. Cramer: Ueber die Beziehung der Kleidung zur Hautthätigkeit, Arch. f. Hyg., 1890, **10,** 231.

11. Nuttall: Ueber den Einfluss von Schwankungen in der relativen Feuchtigkeit der Luft auf die Wasserdampfabgabe der Haut. Arch. f. Hyg., 1895, **23,** 184.

12. Wolpert: Ueber den Einfluss der Lufttemperatur auf die im Zustand anstrengender körperlicher Arbeit ausgeschiedenen Mengen Kohlensäure und Waserdampf beim Menschen, Arch. f. Hyg., 1896, **26,** 32; Ueber die Kohlensäure- und Wasserdampf- Ausscheidung des Menschen bei gewerblicher Arbeit und bei Ruhe, ibid., p. 68; Einfluss der Luftbewegung auf die Wasserdampf- und Kohlensäure-Abgabe des Menschen, ibid., 1898, **33,** 206; Ueber den Einfluss des Windes auf die Atmungsgrosse des Menschen, Arch. f. Hyg., 1902, **43,** 21; Ueber den Einfluss der Luftfeuchtigkeit auf den Arbeitenden, ibid., 1899, **36,** 202. Wolpert and Peters: Die Tageskurve der Wasserdampfabgabe des Menschen, ibid., 1906, **55,** 299.

13. Laschtschenko: Ueber den Einfluss des Wassertrinkens auf Wasserdampf- und CO_2-Abgabe des Menschen, Arch. f. Hyg., 1898, **30,** 145.

14. Rubner, M.: Notiz über die Wasserdampfausscheidung durch die Lunge, Arch. f. Hyg., 1898, **33,** 151. Rubner, M., and Von Lewaschew: Ueber den Einfluss der Feuchtigkeitschwankungen unbewegter Luft auf den Menschen während körperlicher Ruhe, ibid., 1897, **29,** 1.

in the breath during various activities. The subject gave off 17 gm. an hour when quiet, 19 gm. when breathing deeply, 28 gm., reading, and 34 gm. singing. Schattenfroh[15] found that a fat man gave off much more water than a thin man in work experiments, and that with an air temperature of 38 C. and relative humidity of 63 per cent., the heat elimination was not sufficient to prevent a rise of body temperature. Rubner[16] makes some important calculations as to the amount of water a man in the tropics must drink in order to provide enough urine to dissolve the urea and also enough sweat to keep the man cool. It is obvious that with an air temperature of 38 C. or higher, vaporization is the only means of dissipating heat from the body. In order that heat may be dissipated, a man requires 4,400 gm. of water on the ordinary European diet, if producing 2,400 calories per day. On an exclusive meat diet he would require 7,600 gm. of water.

A large amount of data in regard to the water elimination of man can be found in the publications of Atwater, Benedict and their associates.[17] These investigators used a large Atwater-Rosa calorimeter in which a man lived for periods of half a day to two weeks. The experiments were not planned as a study of the water elimination, but they are of great value on account of their length and completeness.

The results are summarized by Benedict and Carpenter[18] who have corrected some miscalculations of the earlier publication. The temperature of the calorimeter was about 20 C., and the humidity in the rest experiments comparatively low. In the work experiments, however, the rate of ventilation was not sufficient to prevent a rise in humidity until it reached a point where there was condensation on the cold-water pipes in the ceiling. These helped to remove the moisture from the air and the water which dripped from them was collected and weighed by the subject of the experiment. The relative importance of the various channels of heat loss are calculated by Benedict and Carpenter and also the changing percentage of calories lost in vaporization with different degrees of muscular activity.

15. Schattenfroh: Respirationsversuche an einen fetten Versuchsperson, Arch. f. Hyg., 1900, **38,** 93.

16. Rubner, M.: Vergleichende Untersuchung der Hautthätigkeit des Europaers und Negers, nebst Bemerkungen zur Ernährung in hochwarmen Klimaten, Arch. f. Hyg., 1900, **38,** 148.

17. Atwater, W. O., and Benedict, F. G.: Experiments on the Metabolism of Matter and Energy in the Human Body, U. S. Dept. of Agriculture, Bull. 136, 1903, pp. 95 and 134. Benedict, F. G.: The Influence of Inanition on Metabolism, Carnegie Institution of Washington, Pub. 77, 1907. Benedict, F. G., and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Man During Rest, ibid., Pub. 126, 1910. Benedict, F. G.: A Study of Prolonged Fasting, ibid., Pub. 203, 1915.

18. See Note 17.

TABLE 5.—Apportionment of Heat Loss

	Rest	Work
Radiation and conduction	75.3	45.5
To warm inspired air	2.0	
Heat of urine and feces	0.7	0.4
Water vaporized from lungs	9.8	43.6
Water vaporized from skin	12.2	
Heat equivalent of external muscular work	....	10.5

TABLE 6.—Percentage of Calories Lost in Vaporization

Condition of Activity	Number of Subjects	Heat Eliminated, Cals.	Percentage of Calories Lost in Vaporization
Rest	5	2,390	22.8
Moderate work	2	2,708	30.9
Severe work	3	4,813	39.6
Very severe work	2	8,225	47.6

Benedict,[19] in his first work on inanition, reviews the literature on the water elimination in fasting. He found that the greatest output took place in the waking hours, and that the amount of drinking water had no effect on the amount eliminated. Benedict calculates the water elimination from the lungs by estimating the volume of the respired air and determining the amount of water required to raise its water content to saturation at body temperature. He found that in most experiments the water elimination from the lungs was somewhat less than from the skin. In the second publication on inanition[19] it is possible to follow the water elimination through a long period of fasting, the subject spending each night in a small bed calorimeter at a temperature of about 21 C. He calculates the water vaporized from the lungs as 9.6 to 10.7 gm. per hour, or from 40 to 65 per cent. of the total.

Day of Fast	Relative Humidity	Water Vaporized Gm.
1– 3	52–63	23–29
17–20	39	15–16
27–30	42–49	18–20

19. See Note 17.

Benedict and Joslin[21] studied a number of diabetics in the same calorimeter and give the following figures for the percentage of calories lost in vaporization:

	Per Cent.
9 Normal controls	22.5
4 Severe diabetes	24.0
3 Light diabetes	22.1

In addition to the series of papers from the laboratories of Rubner and Benedict there have been a large number of scattered publications dealing with the water of vaporization. Only a few can be reviewed in this communication. Janssen,[22] in 1883, studied the water elimination from the arms and legs of normals and nephritics and found that vaporization was increased over edematous parts. Masje[23] investigated the radiation of heat from small areas of skin in different parts of the body. Erismann[24] placed the arm in a box and determined the influence of various factors. Von Willebrand[25] used a cabinet which collected the moisture from the skin only, the head of the subject projecting out of the apparatus. With a relative humidity of 40 to 50 per cent. and a temperature of 12 C., 10.5 gm. water per hour were given off by the skin; at 18 C., 13 to 18 gm.; at 28 C., 26 to 27 gm. There was a sudden outbreak of sweat in one case when the temperature reached 30 C.; in the other man, when it rose to 33.5 C. The carbon dioxid elimination from the skin was constant at 0.2 to 0.4 gm. per hour until the outbreak of sweat, when there was a marked rise in the elimination of this gas. Von Willebrand concludes that before the outbreak of visible sweat the so-called *insensible* perspiration was chiefly vaporization from the outer layers of the skin and not the secretion of the sweat glands. Schwenkenbecker[26] used a similar form of apparatus and confirmed the work of von Willebrand on normals. He studied patients with exophthalmic goiter, tuberculosis, nephritis, diabetes, pneumonia, ichthyosis and several other conditions. He deter-

21. Benedict, F. G., and Joslin, E. P.: Metabolism in Diabetes Mellitus, Carnegie Institution of Washington, Pub. 136, 1910.

22. Janssen: Die Hautperspiration beim gesunden Menschen und bei Nephritikern, Deutsch. Arch. f. klin. Med., 1883, **33,** 334.

23. Masje: Untersuchungen über die Wärmestrahlung des menschlichen Körpers, Arch. f. path. Anat., 1887, **17,** 267.

24. Erismann, E.: Zur Physiologie der Wasserverdunstung von der Haut, Ztschr. f. Biol., 1875, **11,** 1.

25. Von Willebrand, E. A.: Ueber die Kohlensäure- und Wasserausscheidung durch die Haut des Menschen, Skand. Arch. f. Physiol., 1902, **13,** 337.

26. Schwenkenbecker, Dr.: Ueber die Ausscheidung des Wassers durch die Haut von Gesunden und Kranken, Deutsch. Arch. f. klin. Med., 1904, **79,** 29. Schwenkenbecker and Tuteur: Wie reagiert der fiebernde Mensch auf eine willkürliche Steigerung seiner Wärmebildung? Arch. f. exper. Path. u. Pharmakol., 1907, **57,** 285. Schwenkenbecker and Inagaki: Ueber die Schweissekretion im Fieber, ibid., 1905, **53,** 365.

mined the rise in water elimination in typhoid fever after giving certain standard diets and followed the results in various stages of the disease. He concludes that with a rising temperature the vaporization from the skin is at the lower normal limit. With a continued temperature it is somewhat raised, and with a falling temperature it is "active" in proportion to the fall in temperature. In the course of a long-continued fever it becomes gradually smaller. Loewy and Wechselman[27] have made an important contribution in the study of three men born without sweat glands. Although they could not sweat, even when exposed to great heat, they were able at ordinary temperatures to lose as much water through the skin as normal controls. Loewy[28] continued the work with normal adults, children, patients with ichthyosis and two who were paralyzed. He found that different parts of the body gave off different amounts per square meter of surface, and that the same part showed large variations at different times. Anything that lowered the temperature of the skin decreased the water elimination. He believes that the insensible perspiration at ordinary temperatures is due to a physical vaporization through the outer skin and not to a secretion of the sweat glands. He confirmed the older observation of Unna that fat rubbed on the skin diminishes the water loss.

Lang[29] studied the influence of food and of tuberculin fever on the water elimination. He gives a good review of the Russian literature.

Staehelin,[30] using a Jaquet respiration apparatus, determined the heat production and water elimination in the night after various standard meals. The percentage of calories lost in vaporization was between 18 and 21 in basal and food experiments. A well planned experiment on a tuberculous patient with nightsweats was almost spoiled by the restlessness of the subject. Niemann[31] gives figures showing the water of vaporization of babies. This determination must present unusual technical difficulties.

Magnus-Levy[32] calculates the amount of water formed in the oxidation of the various foodstuffs as follows:

---

27. Loewy and Wechselman: Zur Physiologie und Pathologie des Wasserwechsels und der Wärmerregulation seitens des Hautorgans, Virchows Arch. f. path. Anat., 1911, **206,** 79.

28. Loewy, A.: Untersuchungen über die physikalische Hautwasserabgabe, Biochem. Ztschr., 1914, **67,** 243.

29. Lang: Beobachtungen über die Wasserausscheidung durch Haut und Lungen unter den Einfluss des Fiebers, Deutsch. Arch. f. klin. Med., 1904, **79,** 343.

30. Staehelin: Versuche über Gaswechsel und Energieverbrauch nach Nahrungsaufnahme, Ztschr. f. klin. Med., 1906, **66,** 201; Der respiratorische Stoffwechsel eines Phthisikers während des Nachtschweisses, ibid., 1906, **66,** 241.

31. Niemann: Der respiratorische Gaswechsel in Säuglingsalter, Ergebn. der inn. Med. u. Kinderh., 1913, **11,** 32.

32. Magnus-Levy, A.: In von Noorden's Handbuch der Pathologie des Stoffwechsels, Berlin, 1906, **1,** 424.

	Gm.	For 100 Calories	
100 gm. fat give	107.1	11.3	
100 gm. starch give	55.5	13.3	Av. 11.3
100 gm. protein give	41.3	9.3	
100 gm. alcohol give	117.4	16.8	

On the ordinary mixed diet of 2,500 calories we should, therefore, obtain about 300 gm. water from the oxidation of the hydrogen in the foods.

The extensive literature on the vaporization of water in fever is not reviewed, but will be discussed in a later communication.

METHODS USED

The Sage calorimeter was built primarily to determine the oxygen consumption, carbon dioxid elimination and total heat production. This latter, as determined by the method of direct calorimetry, is the algebraic sum of the heat of radiation and conduction, the heat stored in or lost from the body as the temperature rises or falls, and the heat rendered latent in the vaporization of water. The air within the calorimeter in all the experiments is between 22 and 24 C., and at this temperature the vaporization of 1 gm. of water requires 0.584 calories. If 1 gm. of water is condensed, the same amount of heat is liberated. For this reason the calorimeter measures accurately the total heat eliminated from the subject, even though some of the water vaporized by the skin be deposited on the walls, pipes or bedding. In such a case, part of the calories which are actually lost from the body by the vaporization of water are transferred to the column of "radiation and conduction." Fortunately, this error is not very large until the humidity reaches a point near 60 per cent., when there is condensation of visible dew on the pipes in the ceiling. The water enters these at a temperature of 13 to 16 C. and leaves them 2 to 4 degrees higher, removing in this manner the heat of radiation and conduction. Their surface area is great and they condense large amounts of moisture from the air when it is saturated at their temperature.

Sometimes the patient is sealed in the calorimeter when the walls and bedding have stood in air at a certain degree of humidity, and then the air is made drier by excessive ventilation. This removes not only the water vaporized from the body, but also a certain amount of moisture from the bedding, etc. More frequently, the humidity rises and moisture is absorbed by the contents of the calorimeter. The subject has been discussed under the heading of "Sources of Error in Technic."

We find ourselves, then, with about 300 experiments on patients and normal controls in which the water vapor removed in the ventilating current of air had been determined in hourly periods. No other

group of observations furnishes so much information as to the water vaporized from skin and respiratory passages in disease. The interpretation of the results must be made with great care on account of the unavoidable technical error.

At the very beginning we must put aside certain experiments and exclude them from the tables used in obtaining averages. The first to be ruled out are those in which the water elimination was so great that there was a condensation of moisture on the cold-water pipes. In this group we find a number of experiments on hyperthyroidism, dyspneic conditions and typhoid fever with falling temperature. These are just the cases in which we should like most to measure the increased percentage of calories lost in vaporization. We must also exclude a few cases with very low water output, because the humidity diminished so rapidly. It seems best to retain only the observations in which the relative humidity did not change more than 10 per cent. and did not approach the point of condensation on the cold pipes. This leaves us 175 satisfactory experiments. Using these, we can compare the normal controls and various groups of patients, because they were studied under certain standard conditions which tend to make the errors constant, thus allowing us to compare the results. These conditions are as follows:

The open calorimeter containing the bed, described in Paper 11, is kept at a temperature of 23 to 24 C. on the night before each experiment, the relative humidity of the air during most of the year being rather low, 15 to 40 per cent. At about half past 9 in the morning the subject is dressed in nightshirt, thick cotton pajamas and two pairs of socks; one pair cotton, one woolen. At about half past 10 he is placed in the calorimeter, the apparatus sealed, and the ventilation adjusted at a rate suitable to the estimated heat production. About an hour later the experiment is started. During this preliminary period the humidity usually rises 10 to 20 per cent., and, after the experiment has begun, continues to increase very slowly.

Before October, 1916, the Crowell blower used on the absorber table could not give a rate of ventilation higher than 70 liters per minute, and this was not sufficient to prevent a slight increase in humidity as the experiment progressed. If the subject had a very high metabolism and water elimination, the humidity would increase to 60 to 70 per cent., at which point there would be a condensation on the pipe which contained the ingoing water at a temperature of 13 to 16 centigrade.

In the summer of 1916 a Lehman Brothers' blower was installed. With this it is possible to obtain any rate of ventilation between 50 and 90 liters a minute. Higher speed would be impracticable with the present system of absorbing bottles. Using this new blower, it is possible to remove 50 to 60 gm. of water an hour and prevent condensation. It is also possible to maintain a low and absolutely uniform

humidity with a normal subject, regulating the ventilation according to the reading of a small hair hygrometer suspended just inside the window of the calorimeter. An experiment performed on E. F. D. B., Dec. 17, 1916, using the newer experimental conditions, in which the humidity was maintained very constant, showed that he gave off 37 gm. of water an hour, losing in this manner 29 per cent. of his calories. With the old blower and lower rate of ventilation and increasing humidity, an average of 31 gm. was removed per hour, and the apparent percentage loss in vaporization was 25 per cent.

An effort has been made to keep the tables expressing the results as small as possible. Only those experiments are used which have already been described in detail, and the first three columns enable one to find the paper of this series in which the data have been published. The relative humidity at the start and finish of each experiment was determined by passing 10 liters of air through a U-tube containing concentrated sulphuric acid. The actual weight of water removed from the calorimeter was determined by weighing the large Williams' bottles half filled with sulphuric acid. Finally, the percentage of calories lost in vaporization was calculated, using the method of direct calorimetry to obtain the total calories. Since the latent heat of vaporization enters into the direct calorimetry, it seemed advisable to use this method of total heat production instead of the method of indirect calorimetry which, after all, gives almost identical results in every group of experiments. Comparisons between various groups are made in the terms of percentage of heat lost in vaporization. This had been the standard method of Atwater and Benedict, and it is the logical method, since the chief function of the vaporization of water is the removal of a certain proportion of the heat produced within the body. We might express the findings in terms of grams of water per kilogram, or square meter of surface area, but this would be of no particular significance in those conditions in which the total metabolism is increased or decreased.

WATER ELIMINATION OF NORMAL MEN UNDER STANDARD CONDITIONS

Thirteen normal men were studied in twenty-nine experiments under the standard conditions (Table 7). They gave off an average of 29 gm. of water an hour, and lost in this manner an average of 24 per cent. of their calories. The percentage figures all come between 21 and 28, and these extremes may be considered as representing roughly the normal limits for the given conditions. It is interesting to note that the only woman studied gave off much more water. This may have been the result of different clothing.

Some of the normal men were given meals containing various

TABLE 7.—Normal Controls

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
E. F. D. B.	3/13/13	4	50	54	27	21	Basal experiments
	5/17/13	4	52	45	32	26	
	3/20/14	4	37	39	31	23	
	5/18/14	4	35	37	28	24	
	5/ 6/15	11	28	35	32	26	
	5/ 7/15	11	44	36	33	26	
	4/12/16	20	43	44	32	23	
	4/26/16	20	41	40	30	27	
John L.	2/26/14	11	38	30	25	24	
	4/ 3/14	11	28	30	24	23	
Charles M.	5/ 4/14	4	36	34	28	23	
Albert G.	12/21/14	11	34	36	32	26	
	12/23/14	11	25	32	26	24	
	12/28/14	11	29	30	26	21	
	1/ 8/15	11	32	37	29	25	
	1/ 9/15	11	38	38	33	28	
Richard S.	4/19/15	11	36	32	26	21	
	4/21/15	11	32	30	25	20	
Morris S.	12/17/14	12	27	23	27	23	
A. F. C.	1/21/15	12	31	33	27	26	
J. H. M.	4/21/16	20	40	41	34	25	
J. C. F.	4/27/16	20	41	34	28	22	
	11/10/16	Unpub.	35	27	25	21	
	11/12/16	Unpub.	38	33	29	24	
J. C. A.	4/20/16	20	35	36	30	22	
S. K.	5/16/16	21	29	32	27	25	
G. F. B.	5/23/16	21	42	37	29	26	
Average					29	24	
Emma W.	5/13/15	13	43	25	30	34	Normal woman
	5/17/15	13	38	34	29	33	

amounts of dextrose or protein, thus increasing the heat production (Table 8). In a few cases the water elimination rose to such an extent that the ventilating current could not prevent a condensation on the pipes. In the majority of cases the table shows that the increase in water was merely proportional to the rise in total heat production. It will be noted that large doses of caffein caused a slight rise in the water of vaporization (Table 9).

TABLE 8.—Normal Men. Heat Production Increased by Giving Dextrose or Protein

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
E. F. D. B.	4/ 1/14	4	37	41	32	23	After 10.5 gm. N.
	5/ 8/14	4	43	41	33	25	After 200 gm. dextrose
	5/15/14	4	36	38	30	23	After 200 gm. dextrose
Charles M.	5/ 6/14	4	45	41	33	26	After 200 gm. dextrose
Albert G.	1/ 4/15	13	29	35	31	21	
	1/ 6/15	13	35	38	33	26	
Morris S.	12/18/14	13	30	34	32	25	After 9.66 gm. N.
S. K.	5/12/16	21	29	35	25	23	After 22 gm. N.
Average					32	23	

TABLE 9.—Normal Men After Caffein

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
E. F. D. B.	4/12/16	20	44	50	37	26	Caffein
	4/25/16	20	40	42	34	25	Caffein
J. H. M.	4/21/16	20	41	53	40	25	Caffein
J. C. F.	4/27/16	20	34	38	38	28	Caffein
J. C. A.	4/29/16	20	30	39	35	28	Caffein
Average					36	26	

TABLE 10.—Boys Aged 12 and 13

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Fabian R. S.	3/20/15	12	33	32	29	28	Basal
J. D. D. B.	3/26/15	12	33	32	26	26	Basal
Raymond M.	4/ 3/15	12	32	34	26	27	Basal
Reginald F.	4/ 5/15	12	37	36	28	27	Basal
Henry B.	4/ 6/15	12	30	38	33	32	Basal
Harry K.	4/ 7/15	12	32	37	27	27	Basal
Arthur A.	4/ 8/15	12	26	24	22	22	Basal
Leslie B.	4/ 9/15	12	30	28	23	27	Basal
Average					27	27	

With the boys 12 and 13 years old it was possible to maintain a very even humidity. Their water elimination was close to the upper limit of the normal adults (Table 10). The group of very old men gave almost exactly the same figure (Table 11). The rate of ventilation was better suited to the low heat production of the boys and old men than to the greater caloric output of the men in the prime of life. A proportional ventilation might have brought the figures even closer together. Two of the dwarfs, Raphael de P. and Pat W., showed no thyroid involvement. These, grouped with the two legless men, gave the same average as the men of normal shape and size (Table 12). The other three dwarfs, with symptoms of hypothyroidism, showed a slight diminution of water elimination.

TABLE 11.—VERY OLD MEN

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Andrew O'C.	5/ 8/16	19	44	40	34	28	Old man
Henry L.	3/13/16	19	39	45	33	26	Old man
Charles H.	5/ 3/16	19	38	34	27	28	Old man
Charles W.	5/ 4/16	19	40	34	26	29	Old man
William C.	3/ 2/16	19	27	32	24	23	Old man
John B.	11/ 4/15	19	24	27	22	26	Old man
Average.....	.....	..	..	..	28	27	

TABLE 12.—DWARFS AND LEGLESS MEN

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Robert L.	12/ 9/14	21	30	29	24	24	Legless man
Harry J.	12/11/14	21	29	27	25	24	Legless man
Harry J.	5/ 5/16	21	35	32	25	28	Legless man
Raphael DeP. ...	3/15/16	21	30	33	22	25	Achondroplastic dwarf
Patrick W.	3/24/16	21	22	29	17	20	Rachitic dwarf
George F.	1/ 7/16	21	20	20	16	20	Pituitary dwarf; cretin (?)
Erwin E.	3/ 6/16	21	16	17	13	21	Cretin (?)
Benjamin L.	4/10/14	14	21	20	11	21	Cretin
	4/22/14	14	19	18	11	24	Cretin

TABLE 13.—Typhoid Fever Patients

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Rectal Temp. at Start, C.	Change During Exper., C.	Typhoid Period
			Start	End					
Morris S.	10/29/13	7	49	49	34	24	39.6	−0.1	Contin. temp.
	11/17/13	7	35	38	25	21	38.5	+0.5	1st relapse, ascending temp.
	11/18/13	7	38	43	28	22	39.7	+0.4	1st relapse, ascending temp.
	12/13/13	7	27	31	19	18	37.1	0.0	8th day, normal temp.
	12/16/13	7	27	32	21	20	37.3	0.0	11th day, normal temp.
	12/20/13	7	33	40	26	16	39.3	+0.5	2d relapse, early steep curve
	12/23/13	7	36	37	26	19	38.0	+0.6	2d relapse, early steep curve
	1/ 2/14	7	26	31	21	26	37.0	+0.1	8th day, normal temp.
	1/27/14	7	31	23	22	19	37.1	−0.1	33d day, normal temp.
Charles F.	11/15/13	7	37	47	31	23	40.0	+0.1	Contin. temp.
	11/29/13	7	43	40	28	24	36.7	+0.5	Early steep curve
	12/26/13	7	38	37	26	20	36.8	0.0	25th day, normal temp.
	12/31/13	7	30	37	25	22	37.1	−0.1	30th day, normal temp.
Howard F.	11/ 7/13	7	31	34	24	23	39.7	−0.2	Ascend. temp.
	11/13/13	7	28	35	23	22	39.8	0.0	Contin. temp.
	11/20/13	7	42	37	27	28	39.2	−0.4	Contin. temp.
	12/ 2/13	7	28	27	18	22	36.8	+0.1	6th day, normal temp.
	12/ 6/13	7	26	27	18	21	37.0	0.0	10th day, normal temp.
	12/18/13	7	26	35	21	21	37.1	+0.1	22d day, normal temp.
	12/30/13	7	31	35	23	23	37.3	−0.1	34th day, normal temp.
Thomas B.	10/15/13	7	34	42	26	20	36.8	+1.0	Late steep curve
	10/21/13	7	37	42	25	28	36.7	−0.1	1st day, normal temp.
Anton K.	10/16/13	7	32	40	22	27	37.0	+0.2	Late steep curve
Edward B.	10/23/14	7	41	28	30	23	38.1	+0.8	1st relapse, early steep curve
	10/27/14	7	36	35	30	26	37.4	+0.5	1st relapse, late steep curve
	11/ 4/14	7	40	37	32	27	37.2	+0.2	4th day, normal temp.
	11/ 6/14	7	28	35	25	22	38.8	+0.7	2d relapse, ascend. temp.
John K.	12/15/14	7	36	42	37	24	39.0	+0.2	Contin. temp.

WATER ELIMINATION OF PATIENTS UNDER STANDARD CONDITIONS

In typhoid fever the heat production is increased 30 to 50 per cent., and this makes it difficult to remove all the moisture from the calorimeter, even if the percentage of heat lost in vaporization be not raised. When the patient's temperature begins to fall there is such an increase in water eliminated from the skin that the humidity of the air rises rapidly, often to the point of condensation on the cooling pipes. For

this reason many typhoid experiments are excluded, leaving only those in which the water output was relatively low. If we group those experiments in Table 13 in which the temperature rose 0.3 to 1.0 C., we find the water elimination was decreased to the lower normal limits, 22 per cent. With a temperature that is stationary or changing only 0.2 C. in three hours, the vaporization is about the same as that of normal men, 24 per cent. With a falling temperature there is an increase which may be very marked. After the first week in convalescence the average figure is low, 21 per cent. The findings of Schwenkenbecker[33] are confirmed.

TABLE 14.—PATIENTS WITH EXOPHTHALMIC GOITER

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Max W.	3/22/14	14	39	48	36	22	Severe hyperthyroidism
	4/ 6/14	14	38	54	35	21	
	4/24/14	14	46	55	37	20	
Edwin T.	3/ 6/15	14	49	42	35	25	Acute, moderately severe
	3/10/15	14	39	40	31	25	
	3/22/15	14	47	51	38	26	
James McE.	3/12/15	14	52	54	43	27	Severe
	3/31/15	14	32	39	32	21	
G. S. L.	4/ 9/14	14	37	43	30	.7	Severe
	4/16/14	14	46	52	27	21	
Peter N.	4/14/15	14	25	25	28	22	Atypical
Anna R.	5/10/13	14	44	54	32	30	Moderately severe
	5/14/14	14	40	38	30	25	
Sarah M.	4/29/14	14	52	50	38	30	Mild
Marion B.	2/ 5/15	14	40	47	36	28	Mild
Margaret L.	4/20/14	14	55	54	41	29	Atypical
Bessie H.	4/ 8/14	14	33	35	27	26	Atypical
	4/13/14	14	25	30	21	22	Atypical
	4/18/14	14	22	22	23	26	Atypical

Very recently some experiments have been made on erysipelas patients, using the improved system of ventilation made possible by the new Lehman blower. In one case the body temperature fell 1.2 C. in eight hours, and the percentage of calories lost in vaporization was 27.

33. Schwenkenbecker and Inagaki: Ueber die Schweissekretion im Fieber, Arch. f. exper. Path. u. Pharmakol., 1905, **53**, 365.

In another case the temperature rose 0.8 C. in six hours and 24 per cent. of the calories were used for vaporization.

Exophthalmic Goiter.—In Paper 14 of this series a table was given showing the water elimination of the patients, and the results were briefly discussed. Reviewing the findings critically (Table 14), it is necessary to rule out a large number of experiments in which the water elimination was so great that the ventilating system could not remove the moisture quantitatively. In some of these there may have been no increase in the percentage of heat lost in vaporization. In others there was undoubtedly a rise in water elimination out of proportion to the increase in radiation and conduction. These are the cases which interest us most and it is unfortunate that we cannot determine the water output. Still there remain ten experiments on four men with severe or moderately severe hyperthyroidism in which the technic was satisfactory. Of these, Dr. G. S. L. showed a diminished water elimination, losing only 19 per cent. of his calories in this manner. The other three, Max W., Edwin T., and James McE., were within normal limits in these experiments. We must remember that it was on account of high water elimination that it was necessary to exclude five out of eight observations on Max W., two out of five on Edwin T., and one out of three on James McE. We may conclude that the water elimination in severe hyperthyroidism is usually within normal limits, occasionally decreased, but very often distinctly increased.

TABLE 15.—PERNICIOUS ANEMIA

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Daniel V.	5/ 9/13	15	40	45	32	27	Hb 25 per cent.
Andrew K.	3/11/14	15	24	32	24	19	Hb 20 per cent.
	3/27/14	15	38	36	29	24	Hb 20 per cent.
Martin C.	5/ 4/15	15	34	32	27	27	Hb 21 per cent.
Bartolo D.	5/15/15	15	19	20	17	19	Hb 44 per cent.
Daniel O'C.	4/26/15	15	29	28	22	30	Hb 40 per cent.

Pernicious Anemia.—Table 15 gives the averages obtained in a series of experiments on patients with pernicious anemia. The average figure, 25 per cent., is almost identical with the standard for normal controls. This shows that the dilution of the blood that is found in severe anemia has no effect on the amount of water vaporized.

TABLE 16.—Cardionephritic Patients

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Armon W.	2/13/15	16	31	34	28	23	Mitral disease; fibrillation
Fred D.	2/15/15	16	44	45	37	29	Mitral disease; decompensated
	2/22/15	16	34	31	25	26	Mitral disease; compensated
Edward M.	2/17/15	16	44	42	37	25	Mitral disease; fibrillation
Charles L.	2/19/15	16	38	48	37	24	Valvular disease; nephritis
Burel P.	3/24/15	16	40	30	32	23	Valvular disease
August F.	5/ 1/15	16	34	31	26	31	Nephritis; fibrillation
William S.	2/10/15	16	25	29	24	21	Adherent pericardium
George M.	4/ 7/13	16	45	46	24	24	Chronic nephritis
	3/24/14	16	30	32	24	25	
	4/ 4/14	16	27	29	23	23	
David K.	3/21/13	16	55	62	36	24	Chronic nephritis
	3/24/13	16	49	50	28	23	
William A.	1/25/15	16	34	35	28	28	Aortic insufficiency
	1/27/15	16	44	36	32	27	
Theodore S.	1/28/14	16	56	54	39	29	Mitral stenosis; fibrillation
	1/30/14	16	52	56	37	29	
	2/ 9/14	16	31	35	22	24	

Cardionephritic and Nephritic Patients.—The results obtained in a series of patients in which the cardiac element predominated over the nephritic are given in Table 16. It will be seen that the water elimination was increased above the normal in almost all who suffered from moderately severe dyspnea, and in several of those with slight or no dyspnea. We should expect the increased rate of ventilation of the lungs to remove more water by vaporization, but it is quite possible that the skin is also more active. The average for the whole group was 26 per cent.

The results in fourteen experiments on nephritic patients are grouped in Table 17. The average figure, 23 per cent., is only slightly below the standard. It is instructive to group the findings according to the leading symptoms (Table 18).

Since the dyspnea must increase the vaporization from the lungs, we are forced to believe that there is a slight diminution in the water elimination from the skin in severe nephritis. Still we must remember that the total eliminated in vaporization is the same as in the case of a normal man. The waterlogged patient whose kidneys excrete perhaps

TABLE 17.—Fourteen Nephritic Patients

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Joseph Un.	3/29/16	22	40	43	35	25	Chronic parench. nephritis
	4/ 5/16	22	43	38	28	23	
	4/10/16	22	29	29	22	16	
Lee H.	12/ 4/15	22	27	31	24	27	Chronic parench. nephritis
	1/ 5/16	22	25	30	21	23	
Edna S.	12/ 1/15	23	22	22	18	26	Chronic parench. nephritis
Adam D.	1/14/16	22	26	30	22	22	Chronic parench. nephritis
	2/ 7/16	22	28	30	22	25	
William S.	12/ 6/15	22	30	34	27	21	Chronic parench. nephritis
John K.	3/ 4/16	22	30	33	24	22	Chronic interstitial nephritis
Isadore R.	1/24/16	22	38	47	18	25	Chronic interstitial nephritis; uremia
Frank C.	2/28/16	22	25	34	24	23	Chronic interstitial nephritis; uremia
John O.	2/ 9/16	22	37	37	22	25	Chronic interstitial nephritis
Mildred C.	12/10/15	22	32	34	27	24	Chronic interstitial nephritis

TABLE 18.—Findings in Nephritic Patients Grouped According to Leading Symptoms

Patients with	Percentage of Calories Lost in Vaporization		
	Cardionephritis Group	Nephritic Group	Both Groups
Marked edema	28	24	25
Slight edema	25	22	23
No edema	26	24	24
Marked dyspnea	28	24	26
Slight dyspnea	23	23	23
No dyspnea	26	23	25
Whole group	26	23	24

100 to 400 c.c. a day, eliminates 700 to 800 c.c. water through skin and lungs. It would be interesting to know exactly the effects of hot packs and hot air baths in this disease. Theoretically, we should expect the greatest water vaporization at the highest temperature and the lowest humidity. With increasing humidity the loss from the lungs should decrease and the visible sweat should increase. Rubner and

his associates repeatedly emphasize the depressing effects of moist warm air and the comparative stimulation of dry air.

Diabetes.—In nine out of a total of twenty-nine basal experiments in severe and mild diabetes the percentage of calories lost in vaporization was within normal limits. In ten, the figures were above normal; in nine, below. We must remember that the extremely low metabolism

TABLE 19.—DIABETES

Name	Date	Details Published in Paper	Relative Humidity		H_2O, Gm. per Hour	Per Cent. Calories Lost in Vaporization	Remarks
			Start	End			
Gerald S.	11/ 9/14	17	24	25	21	24	Severe, D:N 1.53
	11/12/14	17	26	28	24	27	Severe, second fast day
	11/14/14	17	20	22	18	23	Severe, fourth fast day; body dried
	11/16/14	17	30	30	28	35	Severe, sixth fast day; body dried
	11/18/14	17	15	17	14	25	Severe, eighth fast day; body dried
	11/22/14	17	15	17	13	21	5th day of feeding; beginning edema
	11/24/14	17	15	17	14	22	6th day of feeding; slight edema
	11/25/14	17	18	18	15	25	7th day of feeding; slight edema
	11/30/14	17	28	25	21	29	Convalescent
	12/ 2/14	17	30	27	24	36	Convalescent
	12/ 4/14	17	22	22	19	24	Convalescent
	12/ 7/14	17	22	22	19	24	Convalescent
William G.	1/11/15	17	21	20	16	22	Sugar-free; emaciated
	1/15/15	17	32	31	24	31	D:N 2.8; emaciated
	1/22/15	17	19	21	18	21	D:N 3.12; emaciated
Joseph U.	2/ 1/15	17	24	21	18	29	Sugar-free; emaciated
Edward M.	10/30/14	17	31	32	26	27	Well nourished
Felix K.	2/11/14	17	32	32	22	30	Sugar-free
	2/26/14	17	25	31	29	16	Sugar-free
	3/20/14	17	22	27	20	19	Sugar-free
Cyril K.	12/16/15	24	34	41	32	23	Severe diabetes; acidosis
	12/18/15	24	43	35	30	23	Severe diabetes; acidosis
	12/20/15	24	34	25	21	18	Severe diabetes; acidosis
	12/22/15	24	27	27	21	19	Severe diabetes; acidosis
	2/16/16	24	17	20	15	17	Recovering
	3/ 8/16	24	27	28	21	20	Recovering
Joseph D.	11/15/15	24	34	35	28	31	Severe diabetes
	11/17/15	24	29	35	24	30	Severe diabetes
	11/19/15	24	46	45	34	36	Severe diabetes
Anna H.	3/31/16	24	27	24	16	32	Much emaciated
Average.....	.....	..	..	..	21	25	

of most of the starved diabetics was accompanied by a very low water output. This in turn made the humidity of the air in the calorimeter much lower than usual, and normal controls, with the relative humidity of 15 to 25 per cent. found in some of the diabetic experiments, might have shown a water elimination somewhat above the standard of 24.1 per cent. obtained when the humidity was 35 to 50 per cent. For this reason the comparison of the starved diabetics with the normals is unsatisfactory. The results in all the experiments are given in Table 19 and the averages for the different phases of the disease are given in Table 20, omitting experiments in which the body temperature changed more than 0.2 C.

TABLE 20.—AVERAGE VAPORIZATION IN DIFFERENT PHASES OF DIABETES

	Number of Observations	Average Percentage of Calories in Vaporization
Severe Diabetes:		
After recent food	1	25
Basal determination	3	24
Second to eighth day of fast	6	25
Sugar-free Fasting	1	30
Basal (emaciated)	5	26
Mild diabetes:		
Well nourished	3	18

The averages in severe diabetes are almost exactly the same as the normal standard, but the variations are large. The amount of water eliminated from the lungs would depend on the rate of ventilation and would be increased in patients with hyperpnea.

SUMMARY AND CONCLUSIONS

The technic of determining the water eliminated from the skin and respiratory passages of a subject in a respiration chamber is exceedingly difficult. If the humidity of the air in the box rises, moisture will be deposited on the contents of the chamber. If the relative humidity falls, water will be removed which was not eliminated by the subject in the experimental period.

Over three hundred experiments have been made in the Sage calorimeter on patients and normal controls at an air temperature of 22 to 25 C. and a relative humidity usually between 30 and 50 per cent. For purposes of comparison all experiments are excluded in which the relative humidity changed more than 10 per cent. between the start and finish of the observation.

TABLE 21.—Water Vaporization of Different Groups of Subjects Studied Under Standard Conditions of Clothing, Temperature and Ventilation. Summary Table

Group of Subjects	Number of Experiments in Group	Percentage of Calories Lost in Vaporization
13 normal men, ages 22 to 44 years	29	24
6 men after glucose or protein	9	23
4 men after 7 to 10 grains of caffein	5	26
8 boys, ages 12 to 13 years	8	27
6 old men, ages 77 to 83 years	6	27
2 legless men	2	25
2 dwarfs (1 rachitic; 1 achondroplastic)	2	23
3 cretinoid dwarfs	4	22
4 typhoid patients, temperature rising 0.3 to 1.0 C.	9	22
5 typhoid patients, temperature change less than 0.3 C. during experiment	6	24
1 typhoid patient, temperature falling 0.4 C.	1	28
3 typhoid patients, 2d to 8th week of convalescence	9	21
5 pernicious anemia patients	6	25
17 cardionephritics and nephritics	24	24
With marked edema	8	25
With slight edema	5	23
With no edema	8	24
With marked dyspnea	6	26
With slight dyspnea	10	23
With no dyspnea	8	25
8 diabetics	30	25

Normal men 20 to 50 years old under the standard conditions excrete on an average 29 gm. water an hour (about 700 gm. a day) through skin and air passages, losing in this manner 24 per cent. of the total heat produced. Few normal men depart more than one-tenth from this figure. All the results on groups of patients are compared with this standard figure of 24 per cent., plus or minus one-tenth. (Table 21.) Boys 12 to 13 years old give figures close to the upper limit and very old men lose almost the same percentage of calories in vaporization. Dwarfs and legless men are also close to the normal average. Cretinoid dwarfs show diminished water elimination. Typhoid patients with a rising temperature also have a decreased water output; those with a falling temperature lose an increased percentage of calories in vaporization. The water output in convalescence is low.

Some patients with hyperthyroidism have a decreased water out-

put; most of them lose the normal percentage of calories in vaporization. Some lose much more than normals in this manner. In pernicious anemia the water of vaporization is not affected. Cardiac and nephritic patients on the whole give figures close to the normal. There is a slight increase in dyspneic patients. Edema seems to have no effect on the water output through the skin. The results in diabetes show great variations. The average figure, however, is about the same as that obtained in normals.

In conclusion it may be said that the output of water is very little affected in disease. When the heat production is increased the body responds and dissipates the usual percentage of calories in the vaporization of water. When it is necessary to get rid of unusual amounts of heat the percentage lost in vaporization is increased.

477 First Avenue.